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THE BIOLOGIC VALUE, IODINE CONTENT, HISTOLOGIC STRUCTURAL AND CLINICAL PICTURE OF GOITER *

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In 1916, Graham [1] applied the Gudernatsch test to goitrous material of various kinds and showed that a certain definite relationship exists between the iodine and colloid content and the physiologic activity of tadpoles on which the test is made. Since then a great number of similar experiments have been carried out in different countries on every kind of goiter. Particular reference might be made to the work of Wegelin and I. Abelin,[2] of C. Abelin,[3] and of Branovačky [4] on normal and abnormal human thyroid glands of all clinical and histologic groups; of Wydler [5] and of Dubois [6] on the goiters of cretins, and of Branovačky and Pelech [7] on certain malignant goiters. In 1923, Hara [8] applied the Asher-Streuli test on rats to different types of goiter.

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1. Graham, A.: A Study of the Physiological Activity of Adenomata of the Thyroid Gland, in Their Relation to Their Iodine Content as Evidenced by Feeding Experiments on Tadpoles, J. Exper. Med. **24**:345, 1916.

2. Wegelin, C., and Abelin, I.: Ueber die Wirksamkeit der menschlichen Schilddruese im Froschlarvenversuch, Arch. f. exper. Path. u. Pharmakol. **89**:219, 1921; Weitere Untersuchungen ueber die Wirksamkeit menschlicher Kroepfe im Kaulquappenversuch, ibid. **105**:137, 1924.

3. Abelin, C.: Ueber den Jodgehalt von Kroepfen im Vergleich zu ihrer histologischen Struktur und ihrer Wirkung im Kaulquappenversuch, Arch. f. exper. Path. u. Pharmakol. **124**:1, 1927.

4. Branovačky, M.: Die biologische Wirksamkeit verschiedener Kropfarten im Kaulquappenversuch, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **39**:563, 1926.

5. Wydler, A.: Die Histologie der Kretinenstruma, mit Beruecksichtigung der Klinik des Kretinismus und der funktionellen Untersuchung, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **39**:467, 1926.

6. Dubois, M.: Vergleichende Untersuchungen ueber den biologischen Wert des Kretinenkropfs, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **39**:543, 1926.

7. Branovačky and Pelech: Ueber den funktionellen Wert der Langhansschen wuchernden Struma, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **39**:609, 1926.

8. Hara, Y.: Untersuchungen ueber die pathologische Physiologie des Kropfes mittels der Asher'schen Methode der Empfindlichkeit der Ratten gegen Sauerstoffmangel, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **36**:537, 1923.

His findings were confirmed and extended by Branovačky.[9] The conclusions drawn from those investigations of the Bern school were that only within one of the different well defined clinicopathologic groups of goiter does there exist the relationship found by Graham—that goiters with high iodine and colloid content are as a rule more active than those with little colloid and low iodine content. For instance, in endemic, clinically indifferent goiter, the biologic value decreases as follows: diffuse colloid, nodular colloid, diffuse parenchymatous and nodular parenchymatous goiter. These investigators furthermore showed that the biologic value decreases from the goiter in Graves' disease to the goiter in endemic cretinism thus: struma basedowiana; endemic, clinically indifferent goiter and goiter of cretins. The physiologic activity, therefore, does not depend on the quantity of the colloid, and at the present time no chemicohistologic or tinctorial method exists to distinguish, for instance, the colloid of a goiter of a cretin from that of a normally functioning diffuse colloid goiter. Only biologic methods can reveal greater differences between the different groups and reveal finer distinctions between goiters of the same group.

In 1928, Spatz[10] published similar investigations on the Bavarian goiter, which as a whole are in agreement with those of the earlier authors. During the same year, Williamson, Pearse and Cunnington[11] reported experiments on tadpoles with material from various types of goiter. Their results will be discussed later in connection with my findings.

The importance of regional factors that influence the growth and the histologic structure of goiter has been stressed by a great number of authors. The differences are so great that the question arose whether "goiter" is the same in different localities. This doubt, and the question whether a principal biologic difference exists between the diffuse primary exophthalmic goiter and the adenoma with hyperfunction, were the reasons why the experiments reported here were made.

Twenty-nine goiters (seven clinically indifferent adenomas, ten adenomas with hyperfunction, ten diffuse goiters of primary Basedow's disease, one goiter with hypofunction and one normal gland with a few nodules) were examined. The Gudernatsch test on tadpoles was made in all twenty-eight cases, the iodine determinations in twenty-seven and the Asher-Streuli test on rats in thirteen cases.

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9. Branovačky, M.: Der physiologische Wert der verschiedenen Kropfarten, unter gleichzeitiger Berucksichtigung des biologischen Experimentes und des Jodgehaltes, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **37**:488, 1924.

10. Spatz, H.: Vergleichende klinische, histologische und biologische Studien am Muenchner Kropfmaterial, Deutsches Arch. f. klin. Med. **158**:257, 1928.

11. Williamson, G. S.; Pearse, I. H., and Cunnington, H. M.: The Two Products of Thyroid Activity, J. Path. & Bact. **31**:254, 1928.

HISTOLOGIC CLASSIFICATION

Wegelin's [12] classification, the introduction of which was recommended by Marine,[13] is used with slight alterations taken from the classification of Aschoff and Buerkle-de la Camp [14] which is very similar. In order to avoid any misunderstanding, the main points are given here:

I. Struma diffusa
  1. Struma diffusa colloides (macrofollicularis)
    (*a*) Non proliferans (stationary type, with enlarged, evenly round follicles)
    (*b*) Proliferans (proliferating type with numerous "Sanderson'schen Polstern," i. e., epithelial intrafollicular proliferations)
    (*c*) Basedowificata (islets of "hyperplasia" between the follicles)
  2. Struma diffusa basedowiana

II. Struma nosoda (adenoma)
  1. Struma nosoda parenchymatosa
    (*a*) Struma nodosa trabecularis
    (*b*) Struma nodosa tubularis
    (*c*) Struma nodosa microfollicularis (majority of follicles less than 75 microns in diameter)
  2. Struma nodosa colloides
    (majority of follicles more than 75 microns in diameter)
    (*a*) Struma nodosa colloides non proliferans
    (*b*) Struma nodosa colloides proliferans
    (*c*) Struma nodosa colloides basedowificata

III. Struma diffusa combined with struma nodosa

The chief possibility for misunderstanding lies in the fact that Wegelin considered nodule and adenoma synonymously, a point as yet still questioned by other authors. Wegelin based his conception on the fact that nodules show the main characteristic of adenomas, i. e., new growths, namely, the autonomy of growth, and on the fact that they grow from within, often destroying normal tissue by compression. He pointed out that the classification is empiric and that many transitional forms exist that are difficult to identify. This is especially true in the early stages of adenoma formation as different stages often occur in the same gland.

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12. Wegelin, C.: Schilddruese, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8.

13. Marine, D.: The Essential Thyroid Changes in Goiter, Arch. Path. **10**:164 (July) 1930.

14. Buerkle-de la Camp: Einteilung der strumoesen Erkrankungen der Schilddruese von pathologisch-anatomischen Gesichtspunkten aus unter Beruecksichtigung ihrer klinischen Erscheinungen, Arch. f. klin. Chir. **130**:207, 1924.

METHODS

The material was received shortly after the operation. Size, weight and macroscopic appearance were noted. Small pieces were cut out for histologic examination from different parts in order to obtain a complete picture of the structure. The material, fixed in physiologic solution of sodium chloride, three parts, and formaldehyde 40 per cent, U. S. P., one part, was embedded in paraffin and the sections were stained with hematoxylin and eosin and after the method of van Gieson. The results of the histologic examination were compared with those obtained at the department of pathology, University of California Hospital, and proved to be in agreement with each other. The goitrous material was chopped. Extreme care was taken to eliminate in adenomas all calcified and fibrous tissue, hemorrhages and adherent normal tissue. Thus only the active parenchyma was used for the experiments and the iodine determinations. The material was then dried and ground to an extremely fine powder and kept in sterile bottles. It is of decided advantage to work with dried material (independence of time, possibility of repeating experiments, accurate dosage, etc.).

The iodine determinations were made by Mr. J. B. Dalton, of the department of biochemistry, University of California. Kendall's method in the modification of Kelly and Husband [15] was used.

The tests on the tadpoles were carried out in August, September and October, 1929, and from April to the beginning of September, 1930. Second year tadpoles of the species Rana catesbiana were used exclusively. This large species, measuring from 110 to 155 mm. in length, has many advantages, since it is much easier to follow the details of the metamorphosis and to obtain exact measurements. As this species completes metamorphosis in two years, a full scale of effects can be obtained by feeding goiters of different activity. The normal controls metamorphose so slowly that differences in animals fed with material of very low physiologic activity can be detected. Thus no goiter was found that failed to influence the metamorphosis. Preliminary experiments showed that the animals were much more sensitive to the active substances when the metamorphosis had already started, which is in agreement with the experiments made by different authors (Wegelin and Abelin, Branovačky, Dubois and others). Therefore only animals with hindlegs of from 12 to 16 mm. in length were used. Eight series of experiments were made, each including from three to six goiters and two controls. The animals used in one series were all from the same locality and had therefore lived under the same conditions. In two cases in which outstanding results were obtained the experiment was repeated with satisfactory conformity. Four animals were used for each goiter and the same number for each control. The animals were kept in glass tanks containing 2,000 cc. of city tap water in the middle of a well lighted room but were not exposed to direct sunlight. The water was changed every day, and to avoid changes of temperature only water that had been kept for twenty-four hours in the same room was used. All the other precautions outlined by Branovačky [4] were taken. The animals were fed every other day with 0.2 Gm. of the desiccated material. Every other day one control received three tablets of 5 grains of "Tabloid Thyroid Gland, Burroughs and Wellcome" and the other control dried liver. All the animals were fed with finely cut fresh lettuce on alternate days. Three tablets of 5 grains represent 0.972 Gm., or approximately 1 Gm. of fresh gland. Since on an average the dry material equals one fifth of

15. Kelly and Husband: Biochem. J. **18**:951, 1924.

the weight of the fresh gland or goiter, 1 Gm. of normal standardized thyroid gland as contained in three tablets is equivalent to 0.2 Gm. desiccated goiter material.

All results were compared with the effect obtained by this highly standardized product. Thus all the factors that might influence the course of the metamorphosis, such as different season, different temperature and different local origin of the animals, were eliminated. Each day's food was left in the tanks fully twenty-four hours. As the temperature in San Francisco is relatively low during the summer months (rarely 80 F.), fermentation almost never occurred. The animals were fed with the same amount of desiccated material until they died. Measurements (total length, width, length of legs and tail, width of mouth) were taken at the beginning of the experiments, then twice a week thereafter, and just before fixing the animals in Bouin's fluid. The course of the metamorphosis such as appearance of "violin-shape" (Geigenform), loss of the horny jaws and the appearance of the forelegs was recorded daily. At the end of the experiments photographic pictures of the tadpoles were made.

EVALUATION OF THE RESULTS

Since the metamorphosis takes a much longer time with Rana catesbiana, unfortunately the scheme of Branovačky [4] cannot be applied. Instead, diagrams like those shown were made in each case demonstrating clearly the course of the metamorphosis. The curve, which is obtained by subtracting the average length of the hind legs from the average length of the tails, is especially characteristic as it correlates both factors, the influence on the growth of the legs and on the reduction of the tail. The difference in the activity of the various specimens could thus be estimated as early as at the time of the third measurement. Unfortunately, for lack of space, it is impossible to publish all the diagrams. But they revealed, in agreement with the results of the earlier workers, that the average time of death is in a constant relationship to the course of the metamorphosis, as evidenced by the character of the curve, by the average time of the appearance of "violin-shape" and forelegs and by the average time of the loss of the horny jaws. As the effect of the standard product of Burroughs and Wellcome varied in different series due to seasonal and other factors, a correction had to be made. This was done by subtracting the average time of death of these animals from the average time of death of the animals fed with goiter material. Thus for goiters that were more active than the thyroid substance I used a minus sign and for those that were less active, a plus sign. This gives a rather accurate picture of the degree of the effect on the tadpoles.

THE ASHER-STREULI TEST ON RATS

The Asher-Streuli test is based on the fact that rats after having been given injections of, or fed with, thyroid substances become more sensitive to a deficiency of oxygen produced by evacuation. This

increase of sensitiveness is in a constant relation to the quantity and the physiologic value of the fed material. Details are given by Duran,[16] Asher and Streuli,[17] Hara,[8] Branovačky[9] and de Quervain.[18]

The method outlined by Branovačky[9] and not the original one by Hara[8] was mainly followed. Only full grown rats were used for the tests. The average of the four typical reactions (excitement, dyspnea, half lying [halbe Bauchlage] supine [schlaffe Bauchlage]) were determined before and after the feeding, using from twenty-three to twenty-four minutes for evacuation. The course of the evacuation was always strictly the same: from two to three minutes to 660 mm. of mercury and then four minutes for each following 100 mm. The average reaction of the normal animal was found greater with 300 mm. than in the animals used by Branovačky, the maximum and minimum being 318 and 286 mm. Death occurred frequently below 180 mm. The evacuation was discontinued at this pressure and not at 160 mm. as in Branovačky's experiments. Normal atmospheric pressure was reestablished in one and one-half minutes. There was not enough material left from the tadpole experiments for the rat tests in all cases. Only thirteen cases were tested, and a different method of feeding had to be worked out. Since all the manifestations of the administration of thyroid substances appear only after a certain latent period, the time of feeding was prolonged to six instead of three days, and the animals were tested on the seventh day. Thus a higher effect was reached with the same amount of material than when fed during a shorter time. Two-tenths grams of dried goiter material was suspended in 10 cc. physiologic solution of sodium chloride and fed every day by means of a stomach tube. The total amount was therefore 1.2 Gm. One control received three tablets of 5 grains (0.32 Gm.) each of thyroid substance (Burroughs and Wellcome) daily for the same number of days. All tests were made as "blind tests" in order to eliminate any autosuggestion. Neither the clinical and histologic diagnoses nor the effect on tadpoles were known to me at the time the tests were made.

It is clear that the results are immediately comparable among themselves but not with those of the other authors. The values obtained

16. Duran, M.: Das Verhalten von normalen, mit Schilddruesensubstanz gefuetterten und schilddruesenlosen Ratten gegen reinen Sauerstoffmangel, Biochem. Ztschr. **106**:254, 1920.

17. Streuli, H.: Das Verhalten von schilddruesenlosen, milzlosen, schilddruesen- und milzlosen Tieren bei 0_2 — Mangel, zugleich ein Beitrag zur Theorie der Bergkrankheit, Biochem. Ztschr. **87**:359, 1918.

18. de Quervain, F.: Goitre, London, J. Bale Sons & Danielssen, Ltd., 1924; Rueck- und Ausblicke in der Schilddruesen-Pathologie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **39**:415, 1926.

are somewhat lower than those of Branovačky. Instead of applying his evaluation of one plus for each 40 mm., the increase of reaction in millimeters of mercury is given in the charts. The accuracy of the method is about ± 20 mm.

I. GOITER WITH HYPOFUNCTION

CASE 33.—G. P., a housewife, aged 30, lived in California all her life (0-17 Sierra Nevada, goiter region, 17-30 in San Francisco). She had a goiter of six months' (?) duration. She showed symptoms of hypofunction such as nervousness, hot flushes, dry skin and loss of hair. The basal metabolic rate was minus 19 per cent.

The removed tissue weighed 40 Gm. and consisted of two pieces, 5.5 by 4 by 2 and 6 by 3.5 by 2 cm. The cut surface showed a number of small colloid nodules. The surrounding tissue also showed an increase in colloid content. In this case the nodules were not separated from the other tissue, as the capsules were very thin.

Microscopic examination of the adenomas showed large follicles with moderately deep staining colloid and flat nonproliferating epithelium. Hemorrhage was present in some places. The fibrous tissue was increased in some of the nodules. The surrounding thyroid tissue showed large to very large follicles, with medium staining colloid and flat epithelium.

The histologic diagnosis was struma diffusa colloides et nodosa colloides macrofollicularis nonproliferans.

The tests showed:

Iodine content, 0.148 per cent of dry substance.
Effect on the tadpoles, medium (no. 33 in fig. 12).
Effect on the rat, + 38 mm. of mercury.

The deviation in the results of the two tests is very striking in this case. In the Gudernatsch test the gland was more active than all the clinically indifferent and all the slightly hyperactive adenomas, but the figure obtained in the Asher-Streuli test was the lowest of all the goiters. Again it must be emphasized that the latter was done as a "blind test." Since in the Asher-Streuli test the influence of the thyroid substances on the gaseous exchange of the rat is measured, the low figure of plus 38 mm. would correspond with the low basal metabolism rate of minus 19 per cent. It is impossible to explain findings like this merely by a lack of thyroxin. The assumption of Oswald, de Quervain, Asher and other authors that the thyroxin is not the only product of secretion of the thyroid gland would seem indicated unless one assumes that the quality of the thyroxin is changed.

II. CLINICALLY INDIFFERENT ADENOMAS

CASE 1.—H. G., a housewife, aged 23, lived in England 0-1, in Canada 1-17 and since in San Francisco. She first noticed the goiter from five to eight years before the operation, and about one year before it started to grow rapidly. No symptoms of hyperfunction were present.

The removed tissue weighed 30 Gm. and consisted of two adenomas, one 4 by 3 by 2.5 cm., the other 1 cm. in diameter, which were joined together by some fibrous tissue. Some compressed thyroid tissue was adherent. The cut surfaces of the adenomas showed old and new hemorrhages and calcifications.

Microscopic examination showed that in most of the sections the adenomas contained small follicles, filled with medium staining colloid and lined by flat epithelium. The fibrous tissue was considerably increased throughout the tumor. In some areas the follicles were medium in size, and were filled with medium staining colloid. Here the epithelium was also flat and proliferated in places. In many follicles the signs of old and recent hemorrhage and collections of lymphocytes were present.

The histologic diagnosis was struma nodosa parenchymatosa microfollicularis et nodosa colloides macrofollicularis partim proliferans.

The test showed:

Iodine content, not determined.
Effect on the tadpoles, little.
Effect on the rat, not determined.

CASE 3.—K. P., a man, aged 58, lived in Canada 0-15, in Ohio 15-34, and for the last twenty-four years in San Francisco. He first noticed his goiter about five years before the operation. From three to four years afterward he noticed symptoms suggestive of hyperfunction such as nervousness, irritability, feeling of warmth and increased appetite. These symptoms subsided from three to four months previous to the operation. The patient suffered from generalized arteriosclerosis (blood pressure 230 systolic and 110 diastolic) and chronic nephritis. He was treated with potassium iodide (quantity unknown) some time before the operation.

The removed tissue consisted of one immense, single, well encapsulated adenoma weighing 184 Gm. and measuring 9 by 7 by 6 cm. The cut surface showed one cyst, 2 cm. in diameter, with rather recent hemorrhage. The tissue was yellowish gray.

Microscopic examination of the specimen did not show normal thyroid follicles. In many parts the epithelium formed closely packed sheets, in other parts typical trabecules, separated by hyaline fibrous tissue and capillary vessels. The whole adenoma was well vascularized. In many parts the vessels were considerably distended. The parenchyma cells showed a rather pale staining; round nucleus.

The histologic diagnosis was struma nodosa parenchymatosa partim trabecularis.

The tests showed:

Iodine content, 0.0390 per cent of dry substance.
Effect on the tadpoles, very little (no. 3, fig. 11).
Effect on rat, + 60 mm. of mercury (average of three determinations).

CASE 4.—L. N., a housewife, aged 43, lived in San Francisco during the last thirteen years. She had a goiter of twelve years' duration which increased rapidly during pregnancies. No definite symptoms of hyperfunction were present. The patient showed slight nervousness and slight tremor; also moderate tachycardia which could be due to the beginning menopause. She gained about 48 pounds (21.8 Kg.) during the last four or five years.

The removed tissue weighed 42 Gm. and consisted of two large pieces 7 by 4 by 2 and 5 by 3 by 2 cm. The latter, a well encapsulated adenoma, was used in the experiment.

Microscopic examination of the specimen showed that the follicles in many places were medium in size with medium to deeply staining colloid and flat epithelium with no signs of proliferation. In other parts the follicles were very small with dark staining colloid and flat epithelium. The fibrous tissue was greatly increased throughout the adenoma.

The histologic diagnosis was struma nodosa macrofollicularis non proliferans et nodosa parenchymatosa microfollicularis.

The tests showed:

Iodine content, 0.0344 per cent of dry substance.

Effect on the tadpoles, very slight, atypical (no. 4, fig. 11).

Effect on the rat, not determined.

CASE 6.—D. R., a high school student, aged 19, lived in an endemic goiter region all his life. The goiter started to grow eleven years before the operation, gradually increasing in size. The patient had had a feeling of pressure and slight dyspnea at times, but no other symptoms.

The removed tissue weighed 197 Gm., and consisted of two large masses and some smaller adenomas, 12.5 by 6 by 4.5 and 9 by 5.5 by 4 cm. The larger pieces were lobulated in three parts. One proved to be a cyst filled with blood, but the other was of firm consistency with a rather uniform cut surface. Some new and old hemorrhages as well as calcifications were present. The smaller adenomas showed the same macroscopic picture.

Microscopic examination showed that the picture varied to a great extent. In some parts the follicles were large, with medium staining colloid and with flat to low nonproliferating epithelium. In other parts the epithelium of large follicles showed intensive proliferation. The papillae were so tall that the follicles resembled the uterine tube. In still other parts the follicles were very small with deeply staining colloid, embedded in rather wide, partly hyaline septums of fibrous tissue. New and old hemorrhage and calcifications were present throughout the sections.

The histologic diagnosis was struma nodosa colloides macrofollicularis proliferans et nonproliferans et nodosa parenchymatosa microfollicularis; partim cystica.

The tests showed:

Iodine content, 0.0323 per cent of dry substance.

Effect on the tadpole, minimal, atypical (no. 6 in fig. 11).

Effect on the rat, not determined.

CASE 19.—G. S., a housewife, aged 49, lived in Minnesota 0-23, in Portland, Ore., 23-33, and for the last sixteen years in California (bay region). The goiter developed after childbirth, twenty-five years before the operation. Symptoms of pressure were present but no symptoms of hyperfunction.

The removed tissue weighed 235 Gm., and consisted of three pieces, 12 by 9 by 6, 6 by 5 by 4 and 7 by 7 by 4 cm. The cut surfaces showed similar appearance: wide septums of fibrous tissue lobulate the adenomas, some of which proved to be cysts. The other ones were very rich in colloid.

Microscopic examination of the specimen showed that the great majority of the follicles were large to very large in size, filled with medium staining colloid and lined by flat epithelium. In some parts the epithelium showed proliferation, and in these regions smaller follicles with cuboidal epithelium and medium staining colloid were present. Old and new hemorrhage, considerable fibrosis and calcifications were present in many parts.

The histologic diagnosis was struma nodosa colloides macrofollicularis partim proliferans (fig. 9).

The tests showed:

Iodine content, 0.0372 per cent of dry substance.
Effect on the tadpoles, very slight (no. 19 in fig. 11).
Effect on the rat, + 50 mm. of mercury.

CASE 24.—P. C., a housewife, aged 68, lived in Sweden 0-12, in Chicago 12-22, and ever since in San Francisco. The duration of the goiter was five years. One year before the operation, the patient noticed symptoms of pressure and dyspnea. No symptoms of hyperfunction were present. The dry skin and loss of hair were probably due to senium and not to hypofunction of the thyroid gland.

The removed tissue weighed 75 Gm., and consisted of several small pieces. They were divided by coarse fibrous septums into large and small lobules varying in size from 0.5 to 3 cm.

Microscopic examination showed that the nodules were surrounded by wide tracts of fibrous tissue which contained mostly very large follicles filled with pale colloid and lined by flat to cuboidal epithelium. Proliferations were missing in many sections. In other parts they were predominant, forming papillae. Here small follicles were present.

The histologic diagnosis was struma nodosa colloides macrofollicularis partim proliferans.

The tests showed:

Iodine content, 0.0501 per cent of dry substance.
Effect on the tadpoles, medium (no. 24 in fig. 12).
Effect on the rat, not determined.

CASE 25.—H. N., a housewife, aged 55, lived in Illinois, Omaha and St. Louis, and during the last twenty-seven years in San Francisco. She first noticed her goiter thirty-five years before the operation. She was nervous for the last ten years. No signs of hyperfunction were present.

The removed tissue consisted of three large pieces, 6 by 6 by 4.5 and 7 by 5 by 4 and 4 by 2 by 1.5 cm. They were roughly encapsulated. The cut surfaces showed numerous nodules measuring from 0.5 to 1.5 cm. in diameter. Hemorrhage, new and old, and calcifications were present. The first mentioned adenoma was used in the experiments. It weighed 65.5 Gm. Only 30 Gm. of parenchyma were obtained.

Microscopic examination of some of the nodules showed medium to large sized follicles with medium to deeply staining colloid and flat nonproliferating epithelium. In others the follicles were small with little or no deeply staining colloid and flat epithelium. In many parts they were embedded in partly hyaline fibrous tissue. Lymph cell infiltrations were present in both types of nodules. Signs of hemorrhage were seen in both septums and follicles.

The histologic diagnosis was struma nodosa colloides macrofollicularis non proliferans et nodosa parenchymatosa microfollicularis.

The tests showed:

Iodine content, 0.0411 per cent of dry substance.
Effect on tapoles, very slight (no. 25 in fig. 12).
Effect on rat, not determined.

The iodine content was found to be lowest in this group. It varied between 0.0323 and 0.0501 per cent of dry substance. These figures are as a whole in agreement with the findings of other authors. It is,

of course, impossible to draw far reaching conclusions from a limited number of cases. However, deviations to both sides and notably small figures as in the goiters of Cleveland, Bern (Switzerland) and Freiburg (Germany) were not found. Graham [1] found the iodine content in various types of adenomas in Cleveland (Ohio) from 0.00 or traces to 0.131 per cent; Schmitz-Moormann [19] in adenomas in Freiburg (area of endemic goiter) from 0.0033 to 0.0848 per cent, and C. Abelin [3] in the struma nodosa parenchymatosa from 0.0025 to 0.0846 and in the struma nodosa colloides from 0.0012 to 0.055 per cent, in Bern.

The failure to find low figures for iodine in goiter in California can be explained by the well known fact that both normal and goitrous thyroid glands are richer in iodine in areas near the sea than in inland regions.

The biologic activity in this group was found to be lowest of the groups studied and in general was parallel to the iodine and colloid content. However, the specimen in case 3 with no colloid was about as active biologically as those in cases 19 and 25, which were both rich in colloid. Furthermore, case 3 proves that the biologically active substances are not only present in the colloid but also in the epithelium, which is in agreement with the findings of Wegelin and Abelin [2] but not with those of Williamson, Pearse and Cunnington.[11] All the adenomas, save that in case 24, induced metamorphosis only a little earlier than the liver fed to the animals of the control series (fig. 8). Although the iodine and colloid content was low, no goiter was found that was entirely inactive, as reported by Graham, Wegelin and Abelin and others. It is impossible to compare the results directly, for the feeding during the experiments reported here was continued for a long period and probably revealed smaller amounts of active substances than the methods used heretofore.

Case 6 is of special interest. The influence on the metamorphosis was atypical. Although the animals were fed during more than two months, the tails showed no reduction and the mouths of the tadpoles with the typical horny jaws were still present at the end of the experiments. Meanwhile the forelegs broke through, and all the legs showed considerable increase in length. This unequal action was present but less marked in case 4 in which the mouths of two animals metamorphosed in the normal way. Both adenomas were poor in colloid and in relative iodine content. Wegelin and Abelin [20] found the same unequal action in different degrees in goiters in Switzerland, not only with adenomas but also with diffuse colloid goiters having, for the

19. Schmitz-Moormann, P.: Zur Strumafrage, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **39**:82, 1926.

20. Wegelin and Abelin (footnote 2, second reference).

locality, approximately normal relative iodine content. They interpret this anomaly as a proof of a dysfunction of certain goitrous thyroid glands. The secretion evidently is not only altered in its quantity but also in its quality.

III. NORMAL THYROID GLAND WITH A FEW COLLOID NODULES

Unfortunately, an absolutely normal gland was not available, but that in case 35 consisted mostly of normal tissue. The capsules of the nodules were so thin that they were not separated, but the whole mass was used for the experiments.

CASE 35.—A. T., a man, aged 42, lived in Montana 0-23 and in the Pacific northwest 23-42. The duration of the goiter is not known. Nervousness was the only symptom that might suggest hyperfunction.

The removed tissue weighed 33 Gm., and consisted of two pieces 4.5 by 3.5 by 2 and 4 by 2.5 by 2 cm. The cut surface showed some small adenomas, from 5 to 12 mm. in diameter, in a normal gland. The follicles were not separated from the other tissue.

Microscopic examination of the small adenomas, separated by a thin capsule of fibrous tissue, showed large to very large follicles with medium staining colloid and flat nonproliferating tissue. In the surrounding tissue the follicles were medium to large, with medium staining colloid and flat epithelium.

The histologic diagnosis was a normal gland with a few nodules (nodosa colloides macrofollicularis nonproliferans).

The tests showed:

Iodine content, 0.193 per cent of dry substance.
Effect on the tadpoles, strong (no. 35 in fig. 12).
Effect on the rat, not determined.

The iodine content can probably be considered about normal. The biologic activity of the mostly normal material was very high, but somewhat lower than the thyroid tablets (Burroughs and Wellcome) of the controls of the same series.

IV. ADENOMAS WITH SLIGHT OR QUESTIONABLE HYPERFUNCTION

CASE 23.—S. J., a housewife, aged 34, lived in Arkansas and Oklahoma 0-25, and during the last nine years in California (Los Angeles and San Francisco). She first noticed her goiter about eight years before the operation. After six years, during a pregnancy, questionable symptoms of hyperthyroidism were present. Six months before the operation they became more definite, and immediately before the operation they were mild. They consisted of nervousness, insomnia, tachycardia (from 80 to 90), hyperhidrosis at times and slight tremor of the fingers.

The removed tissue weighed 83 Gm., and consisted of one major adenoma, measuring 7 by 4 by 2 cm., and several smaller ones. The cut surfaces showed mostly colloid tissue separated by wide septums of fibrous tissue. A few recent hemorrhages and some calcifications were present.

Microscopic examination of the specimen showed that in some parts the majority of the follicles were medium in size with flat epithelium, in many places proliferating, and filled with medium to deeply stained colloid. In other areas

the follicles were small with flat epithelium and mostly dark stained colloid. Wide septums of fibrous tissue separated the adenomas irregularly. Collections of lymphocytes were occasionally present near the septums. Signs of old and recent hemorrhage were seen in some of the larger follicles.

The histologic diagnosis was struma nodosa colloides macrofollicularis proliferans et nodosa parenchymatosa microfollicularis with hemorrhages, fibrosis and calcifications.

The tests showed:

Iodine content, 0.0980 per cent of dry substance.
Effect on the tadpoles, medium (no. 23 in fig. 12).
Effect on the rat, not determined.

CASE 26.—H. M., a housewife, aged 45, lived around the great lakes and in the state of Washington, and for the last few years in San Francisco. The duration of the goiter was thirty-three years; of the symptoms of hyperthyroidism, two years. The symptoms consisted of moderate nervousness, tachycardia (from 96 to 105), palpitation, tremor, perspiration and loss of weight (9 pounds [4.1 Kg.] during the last year).

The removed tissue, composed of two huge pieces measuring 10 by 8 by 3 cm. and 11 by 6 by 4 cm., consisted of different adenomas, showing varying degrees of degeneration. Some formed cysts, filled with brownish fluid; the others were mostly of the colloidal type, but some showed old and new hemorrhages, fibrosis and calcification.

Microscopic examination of the specimen showed that in some parts the majority of the follicles were very large, distended with flat epithelium, intermixed with small areas of small follicles and low cuboidal epithelium. Some of the large follicles were filled with blood. Collections of lymphocytes were frequent and of considerable size. Other parts showed wide septums of partly hyaline connective tissue. Here the majority of the follicles were small with flat epithelium and light colloid. Only a few areas showed low cuboidal epithelium.

The histologic diagnosis was struma nodosa colloides macrofollicularis partim basedowificata with hemorrhages, calcifications and formation of fibrous tissue.

The tests showed:

Iodine content, 0.0672 per cent of dry substance.
Effect on the tadpoles, slight (no. 26 in fig. 12).
Effect on the rat, not determined.

CASE 28.—M. M., a widow, aged 67, a shopkeeper, lived in Missouri until 35 years of age; since then she lived in Stockton, Calif. Her goiter was of twenty years' duration. It grew rapidly during the last three years, and at the same time symptoms of hyperthyroidism developed. They were mild at the time of the operation and consisted of nervousness, palpitation, muscular weakness and diarrhea, but no tachycardia or exophthalmos.

The removed tissue weighed 53 Gm. and consisted of two major portions and some smaller adenomas. The first mentioned measured 6 by 4 by 3.5 and 4 by 2.5 by 3 cm. and were composed of different small adenomas.

Microscopic examination of the specimen showed that in some parts the follicles were of medium to large size with intensely stained colloid and low epithelium, mixed with areas of very small follicles with flat epithelium and medium to lightly stained colloid. In other parts all the follicles were small with flat epithelium, separated by hyaline fibrous tissue. Hemorrhage was present in both follicles and stroma.

The histologic diagnosis was struma nodosa macrofollicularis proliferans et nodosa parenchymatosa microfollicularis.

The tests showed:

Iodine content, 0.0675 per cent of dry substance.

Effect on the tadpoles, medium (no. 28 in fig. 12).

Effect on the rat, not determined.

Case 31.—M. E., a housewife, aged 40, lived in California (Sacramento valley and San Francisco) all her life. The duration of the goiter was eighteen years. Slight symptoms of hyperthyroidism developed six months before the operation, such as nervousness, palpitation, tremor, tachycardia (90) and a basal metabolic rate of plus 4.5 per cent. No exophthalmos was present.

The removed tissue weighed 76 Gm., and consisted of one large, well encapsulated adenoma, measuring 6 by 5.5 by 4 cm and weighing 65 Gm., and two small pieces of normal tissue. The adenoma was used for the experiments.

Microscopic examination of the specimen showed small follicles with little or no colloid, lined by large cuboidal epithelium. The stroma was increased, faintly stained and edematous. The thyroid tissue was of normal structure.

The histologic diagnosis was struma nodosa parenchymatosa microfollicularis in a normal thyroid gland.

The tests showed:

Iodine content, 0.0605 per cent of dry substance.

Effect on the tadpoles, slight (no. 31 in fig. 12).

Effect on the rat, not determined.

The iodine content in the latter four cases ranged between 0.0605 and 0.0980 per cent, which is higher than in the clinically indifferent adenomas. This is of great significance. Schmitz-Moormann [19] showed that the relative iodine content of the normal gland steadily increases with the age of the patient and that frequently the same happens in adenomas. This would explain the fact that hyperthyroidism originating from these tumors appears only in later years, as Plummer [21] and Boothby [22] particularly point out.

The biologic activity on the average was higher than in the first group. However, one clinically indifferent adenoma, that in case 24 with 0.0501 per cent iodine, was considerably more active biologically than any of the goiters with slight hyperfunction. In order to explain this fact, one has to take into account the degree of the function of the normal gland, the counteraction of the other glands with internal secretion, and especially the individual sensitiveness of the autonomous nervous system, factors which are all unknown.

There is no absolute relationship between the iodine content and the biologic activity. The specimen in case 23 with an iodine content of 0.098 per cent is even a little less active than that in case 28 with a

21. Plummer, H. S.: The Function of the Thyroid Gland, Beaumont Lecture, Detroit, Jan. 27, 1925.

22. Boothby, W. M.: Adenoma of the Thyroid with Hyperthyroidism (Thyrotoxic Adenoma), Endocrinology **5**:1, 1921.

content of 0.0675 per cent. Both, however, with high colloid content, are more active than the specimen in case 31 with little colloid. Unfortunately, for lack of material, the tests on the rats could not be made in these cases.

The histologic picture does not show any notable characteristics.

V. ADENOMAS WITH DEFINITE HYPERFUNCTION

CASE 10.—D. P., a housewife, aged 40, lived in Italy 0-28, and in California (Sierra Nevada) 28-49. Her goiter was of twenty years' duration. During the last two years symptoms of hyperthyroidism developed such as a moderate degree of perspiration, tachycardia (from 90 to 100), tremor, recent loss of weight (20 pounds [9 Kg.] in three months), blood pressure 160 systolic 90 diastolic and thyrotoxic myocarditis. Five months before the operation she was treated with "medicine" that made her condition worse (probably iodine).

The removed tissue weighed 158 Gm.; the two major pieces, measuring 9 by 6 by 2.5 and 7.5 by 5 by 2.5 cm., consisted of smaller and larger adenomas.

Microscopic examination of the specimen showed very large follicles with deeply staining colloid and flat epithelium, intermixed with areas of small follicles and tall cuboidal to columnar epithelium. Lymphocytic infiltration was not marked.

The histologic diagnosis was struma nodosa colloides basedowificata.

The tests showed:

Iodine content, 0.147 per cent of dry substance.

Effect on the tadpoles, very strong, typical (no. 10 in fig. 12).

Effect on the rats, plus 98 mm. of mercury (average of three determinations).

CASE 17.—M. B., a man, aged 62, always lived in Mendocino County, Calif. His goiter was of eighteen years' duration. Symptoms of hyperthyroidism developed six years before the operation with nervousness, palpitation, tremor, diarrhea and excessive perspiration. They were severe at the time of the operation. The patient lost weight (32 pounds [14.5 Kg.] during the last five years and 13 pounds [5.9 Kg.] during the last year) in spite of a good appetite. The heart showed auricular fibrillation (pulse from 110 to 120). The blood pressure was 180 systolic and 70 diastolic.

The removed tissue weighed 58 Gm., and consisted of two adenomas, 4 by 3.5 by 2.5 and 5 by 4 by 3 cm.

Microscopic examination of the specimen showed very large follicles with medium staining colloid and low, partly desquamating epithelium. Adjacent were areas with small follicles lined by low cuboidal epithelium. New and old hemorrhages were scattered throughout the tissue; collections of lymphocytes were numerous. There was considerable formation of fibrous tissue. A small piece of thyroid tissue showed normal structure.

The histologic diagnosis was struma nodosa colloides basedowificata in a normal gland (fig. 1).

The tests showed:

Iodine content, 0.249 per cent of dry substance.

Effect on the tadpoles, extremely strong, typical (no. 17 in fig. 12; diagram, fig. 2).

Effect on the rat, + 174 mm. of mercury.

CASE 18.—W. M., a housewife, aged 61, lived in San Francisco during the last few years. The duration of the goiter was not known. Symptoms of hyperthyroidism had been present for two years. The symptoms, which were rather severe,

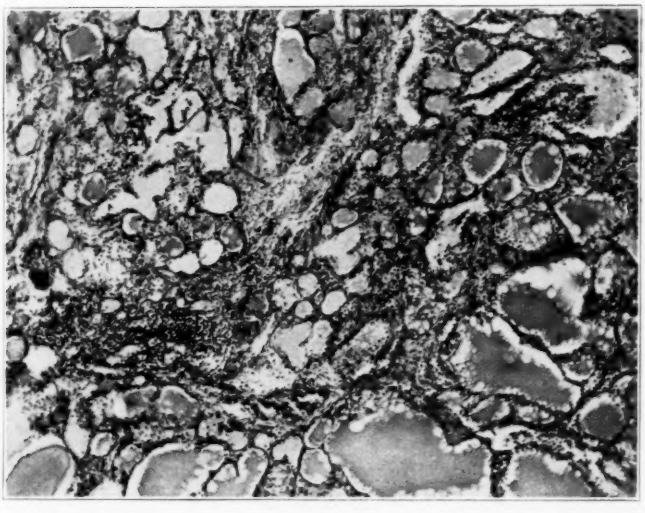


Fig. 1 (case 17).—Struma nodosa colloides basedowificata. In this section are seen medium large and small follicles, formation of papillae in some follicles at the left and collections of lymphocytes. Hematoxylin and eosin; × 75.

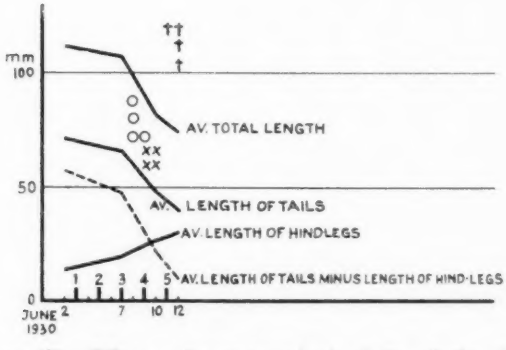


Fig. 2 (case 17).—Effect on the metamorphosis of the tadpoles. Maximum in the group in which adenomas with hyperfunction were used. The iodine content was 0.249 per cent. In this and in figures 4, 6, 7 and 8, the measurements, in millimeters, represent the average of the total length, the length of the tail, and the length of the hind legs of four tadpoles used for one specimen or for one control. The last points on the curves demonstrate the average lengths at the average time of death. The circle indicates the loss of horny jaws; ×, the appearance of the foreleg (l. = left, r. = right), and the dagger, the death of one animal.

consisted of nervousness, palpitation, tremor, excessive perspiration, tachycardia (from 120 to 130), increased appetite, loss of weight (30 pounds [13.6 Kg.] in one and one-half years), blood pressure 180 systolic, 70 diastolic, but no exophthalmos.

The removed tissue weighed 43 Gm., and consisted of four well encapsulated adenomas, 4, 3, 2 and 0.5 cm. in diameter.

Microscopic examination of the specimen showed that the majority of the follicles were very large with flat epithelium, partly desquamated and light to dark staining colloid. Adjacent were areas with small follicles and tall cuboidal or columnar epithelium and faintly staining colloid. Collections of lymphocytes were infrequent.

The histologic diagnosis was struma nodosa colloides basedowificata.

The tests showed:

Iodine content, 0.163 per cent of dry substance.

Effect on tadpoles, very strong, typical (no. 18 in fig. 12).

Effect on rat, not determined.

CASE 27.—J. T., a man, aged 55, lived in New York and Connecticut, and for the last twenty-five years on the seashore of the San Francisco peninsula. He had a goiter of ten years' duration, with symptoms of hyperthyroidism for about one year. The symptoms, consisting of nervousness, palpitations, tremor, excessive perspiration, tachycardia (130 at times) due to thyrotoxic myocarditis with auricular fibrillation, increased appetite and diarrhea, were marked. The patient was treated with compound solution of iodine (10 drops, three times a day) during the three months preceding the operation.

The removed tissue weighed 378 Gm., and consisted of three large pieces, one 11.5 by 8 by 5 cm. composed of many nodules varying in size from 0.2 to 4 cm. Many showed hemorrhages, new and old, and some calcification. One single adenoma measured 8 by 7 by 6 cm., and one piece 6 by 5 by 4.5 cm. showed a structure similar to the first one. The two first mentioned were used in the experiments.

Microscopic examination of the specimen showed that in some sections the follicles were very large with flat, in many follicles proliferating, epithelium and medium stained colloid, mixed with areas of small follicles with cuboidal epithelium. Small collections of lymphocytes were frequent. Some distended follicles showed old and new hemorrhage and others desquamation of the epithelium. In other parts the size of the follicles was more uniform, from small to medium, with faintly staining colloid and flat epithelium. Wide septums of partly hyaline connective tissue, showing signs of old hemorrhage, and some calcifications were present. Lymphocytes were missing in these parts. The histologic diagnosis was struma nodosa colloides partim basedowificata et nodosa parenchymatosa microfollicularis.

The tests showed:

Iodine content, 0.276 per cent of dry substance.

Effect on tadpoles, extremely strong (no. 27 in fig. 12).

Effect on rat, + 149 mm. of mercury.

CASE 32.—B. L., a housewife, aged 33, lived in North Dakota and Idaho; she came to San Francisco two years before the operation for a goiter of eighteen years' duration. It had remained the same size until three years before the operation when, after childbirth, it began to grow rapidly. At the same time symptoms of hyperthyroidism developed, consisting of nervousness, palpitation, excessive perspiration, moderate tachycardia, muscular weakness and loss of weight. No exophthalmos was present.

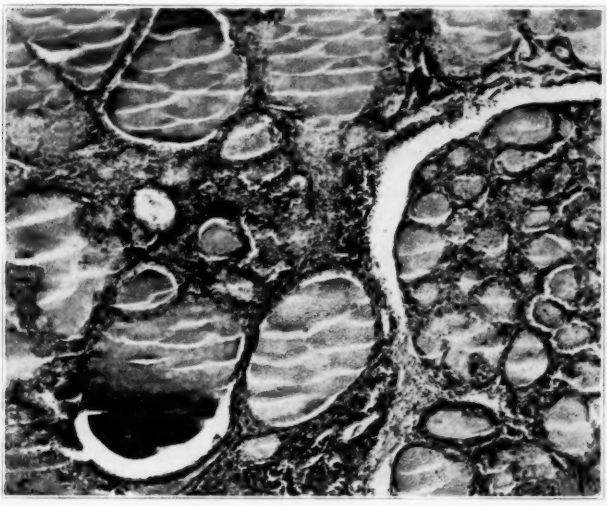


Fig. 3 (case 9).—Struma diffusa basedowiana. The colloid contents in many follicles is greatly increased, as a sequel of a three months' treatment with iodine. Hematoxylin and eosin; × 75.

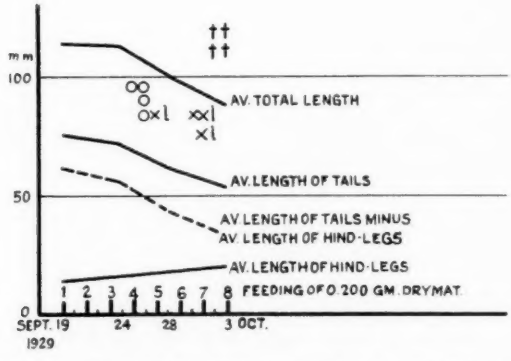


Fig. 4 (case 9).—Effect on the metamorphosis of the tadpoles. Maximum in the group in which struma diffusa basedowiana was used. The iodine content was 0.560 per cent.

The removed tissue weighed 65 Gm., and consisted of two large pieces 5.5 by 4 by 3 and 6 by 3 by 2.5 cm., formed by multiple colloid adenomas of different size. Some showed small calcifications.

Microscopic examination of the specimen showed enormously distended follicles with medium to lightly stained colloid lined by flat epithelium in many parts proliferating in a marked degree. Signs of old and new hemorrhage were present. Between the huge follicles were narrow areas with small follicles, lined by cuboidal epithelium. There were no collections of lymph cells present.

The histologic diagnosis was struma nodosa macrofollicularis proliferans.

The tests showed:

Iodine content, 0.232 per cent of dry substance.

Effect on tadpoles, very strong (no. 32 in fig. 12).

Effect on rat, + 109 mm. of mercury.

CASE 34.—M. L., a housewife, aged 40, an Armenian, lived in California for the last number of years. She had a goiter of eighteen years' duration, which developed after childbirth. Symptoms of hyperthyroidism, consisting of nervousness, tremor, palpitation, excessive perspiration and tachycardia (from 120 to 130) had been present during the last two years. The basal metabolic rate was 20.4 per cent plus, one month before the operation.

The removed tissue weighed 78 Gm., and consisted of two pieces. One measured 5 by 4 by 2 cm. and proved to be normal thyroid tissue. The other, weighing 60 Gm., was a single adenoma, well encapsulated, measuring 6.5 by 4.5 by 3 cm. Only this one was used for the experiments.

Microscopic examination of the thyroid tissue showed a normal structure consisting of medium sized lobules with small to medium large follicles. The colloid was well stained, and the epithelium was flat or low cuboidal. No areas of proliferation or collections of lymphocytes were found. The adenoma showed medium sized follicles with dark stained colloid and flat epithelium. Areas with small follicles were present, with flat to low cuboidal epithelium.

The histologic diagnosis was struma nodosa colloides macrofollicularis partim proliferans in a thyroid gland of normal structure (fig. 10).

The tests showed:

Iodine content, 0.204 per cent of dry substance.

Effect on the tadpoles, very strong (no. 34 in fig. 12).

Effect on the rat, + 124 mm. of mercury.

The relative iodine content varied between 0.147 and 0.276 with an average of 0.2118 per cent, which is second highest of all the groups. The biologic activity, however, was higher in both tests. In case 17 the specimen showed the maximum of all the goiters examined (fig. 2), with the highest iodine content among the untreated (iodine) adenomas. The specimen in case 27 with an iodine content of 0.278 per cent, which had been treated with iodine, was somewhat less active, about the same as the specimen in case 18 with an iodine content of only 0.163 per cent. A definite correlation between the iodine content and the biologic activity on the one hand, and the clinical activity on the other, was not present. However, the goiter with the lowest iodine content and the lowest biologic activity was clinically moderately active, while the goiter in case 17 with the highest biologic activity (fig. 2) was clinically very active. The two localities in which thyroid tablets were used for comparison in the

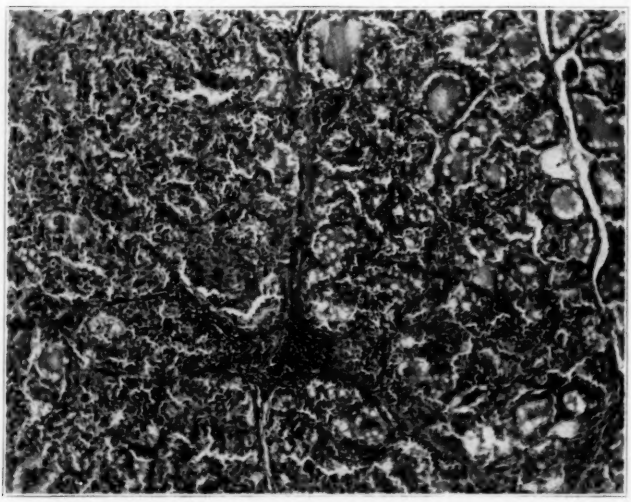


Fig. 5 (case 14).—Struma diffusa parenchymatosa basedowiana. Small follicles with little or no colloid are seen. The duration of the treatment with iodine was nine days. Hematoxylin and eosin; × 75.

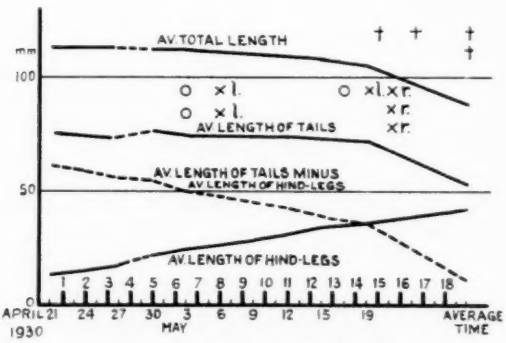


Fig. 6 (case 14).—Effect on the metamorphosis of the tadpoles, very little. In this group struma diffusa parenchymatosa basedowiana was used. The iodine content was 0.196 per cent.

Gudernatsch test, Bern and Munich, are endemic centers. Although both primary and secondary Basedow's disease are much less frequent and milder in areas with endemic goiter than in other sections, often enough cases with symptoms of extreme hyperactivity are observed. The most active adenoma of Branovačky's [4] series, for instance, was from a patient with a basal metabolic rate of plus 52 per cent; the results from this case showed less biologic activity than the thyroid tablets (Parke, Davis and Company) with 0.2 per cent iodine. Some of the adenomas of the series of Spatz [10] were clinically even more active, and in their effect on the tadpoles, as active as the "Thyreoid-Dispert" used as standard. This would therefore suggest that in coastal areas adenomas with hyperfunction are biologically more active, and clinically as active as those in inland areas. Further comparative studies on a larger scale will be needed to verify adaptation of the patients near the sea to a long-lasting hypersecretion.

The average iodine content of the adenomas in Branovačky's series was only 0.0588 per cent, which is well below the iodine content of the normal glands in Bern. The six cases reported here revealed an average of 0.2118 per cent, which is probably as high as in normal glands near the sea, but is about four times as high as in the hyperactive adenomas in Bern.

It is of special interest to note that all the patients with the most active adenomas had lived on the coast for a number of years and that four of six specimens showed basedowification. One patient had been treated with large doses of iodine. The considerably higher colloid content of this group, as compared with the other adenomas, is striking. However, the specimen in case 19 (fig. 9) was rich in colloid, but clinically indifferent and biologically of little activity. This indicates, in agreement with Wegelin and Abelin,[23] that the biologic value depends not on the quantity but on the quality of the colloid. A review of the material of a hundred operations, to be published elsewhere, showed, in agreement with other authors, the same fact, that the struma nodosa parenchymatosa and the colloides et parenchymatosa are clinically less active than the struma nodosa colloides proliferans et basedowificata.

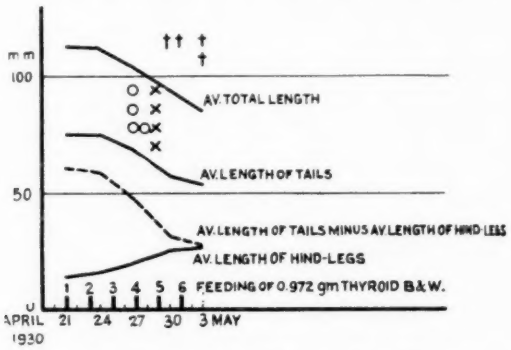
VI. STRUMA DIFFUSA ET NODOSA WITH HYPERFUNCTION

CASE 15.—*N. C.*, a housewife, aged 47, lived in Utah until the age of 42, then in California (in one of the large valleys). She first noticed the symptoms of hyperthyroidism about sixteen months before operation. They became much worse four months after she had undergone an operation (gastro-enterostomy and hysterectomy). The symptoms at the time of the admission to the hospital were typical and moderately severe, consisting of nervousness, palpitation, tremor, hyperhidrosis, tachycardia (from 100 to 130), increased appetite, loss of weight

23. Wegelin and Abelin (footnote 2, second reference). Wegelin (footnote 12).

and exophthalmos. She was treated with compound solution of iodine for thirteen days before the operation (1/6 minim [0.01 cc.] for two days, 1/2 minim [0.03 cc.] for three days and 1/8 minim [0.0075 cc.] for eight days) which relieved her symptoms somewhat.

The removed tissue weighed 72 Gm., and consisted of three pieces measuring 9.5 by 5.5 by 4.5 and 7 by 3.5 by 7.5 and 3.5 by 2 by 1.5 cm., respectively.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1 2 3 4 5 6 FEEDING OF 0.972 gm THYROID B&W.
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Fig. 7 (control no. 7).—Effect of thyroid tablets (Burroughs and Wellcome) on the metamorphosis of the tadpoles, very strong. The iodine content was 0.4 per cent.

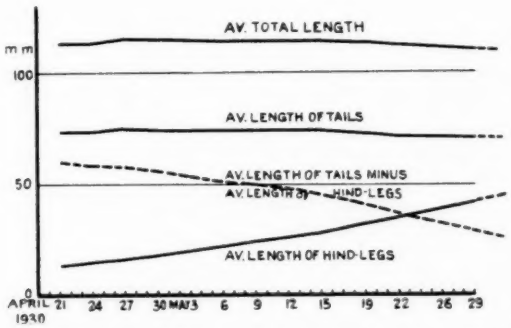


Fig. 8 (control no. 8).—Course of the metamorphosis of normal tadpoles, fed with liver and lettuce. At the end of the experiment all the animals are still alive; they still show the typical tadpole mouth with horny jaws. No forelegs have appeared.

Microscopic examination of the sections showed medium to large follicles with flat nonproliferating epithelium and medium staining colloid, intermixed with areas in which typical proliferations of the epithelium with cuboidal to low columnar cells were present. In still other areas the follicles were small with cuboidal to low columnar epithelium and lightly stained colloid. Collections of lymphocytes were infrequent and small. A few adenomas measuring from 1 to 1.5 cm. were seen, the interior of which showed medium to large follicles with flat nonproliferating epithelium. In the periphery signs of typical basedowification were present.

The histologic diagnosis was struma diffusa colloides basedowificata et nodosa colloides basedowificata.

The tests showed:

Iodine content, 0.296 per cent of dry substance.
Effect on the tadpoles, medium (no. 15 in fig. 11).
Effect on the rat, not determined.

As the capsules of the adenomas in this specimen were very thin, the whole mass was used in the experiments. The biologic activity was, in spite of the high iodine content, low compared with the typical goiters of Grave's disease. This might be due to the inferior biologic value of the adenomas, in which the basedowification evidently started later.

VII. DIFFUSE GOITERS OF PRIMARY BASEDOW'S DISEASE

CASE 2.—W. M., a housewife, aged 29, had a goiter of two years' duration. The symptoms were of moderate degree, but typical, consisting of nervousness, palpitation, tremor, excessive perspiration, increased appetite, tachycardia (from 120 to 130) and exophthalmos. Stellwag, Moebius and Graefe's signs were positive. The patient was treated with the roentgen rays and compound solution of iodine one and one-half years before the operation. The goiter decreased in size, and the patient felt improved. Later the symptoms recurred. Compound solution of iodine was again taken intermittently for fourteen months, but was discontinued some time before the operation. One day before the operation, it was administered again.

The removed tissue weighed 12.5 Gm., and consisted of two pieces, measuring 4 by 2 by 1 and 2 by 2 by 0.8 cm.

Microscopic examination showed the gland to be divided by fibrous septums which were rather wide in places, into small to medium sized lobules. The follicles were small to medium in size, lined by high cuboidal to columnar epithelium. The colloid was mostly pale staining with vacuoles and serrated edges. Lymphocytic infiltration was marked.

The histologic diagnosis was struma diffusa parenchymatosa basedowiana.

The tests showed:

Iodine content, not determined.
Effect on the tadpoles, medium
Effect on the rat, not determined.

CASE 5.—R. E., an unmarried woman, aged 48, lived in California (bay region) all her life. She first noticed the symptoms six months before the operation. They were moderate, consisting of nervousness, palpitation, tremor, hyperhidrosis, tachycardia (from 100 to 110) and muscular weakness, but no ocular symptoms. The patient was treated with compound solution of iodine one month prior to the operation.

The removed tissue weighed 24 Gm., and consisted of two pieces 6 by 4 by 1.5 and 5 by 2.5 by 1.5 cm.

Microscopic examination showed medium to large follicles, lined by flat to low cuboidal epithelium and filled with mostly deep staining colloid. Throughout the sections there were areas with very small follicles, containing little vacuolated colloid with desquamated epithelial cells. Here the epithelium was high cuboidal to columnar. Discrete areas of lymphocytes were rather infrequent.

The histologic diagnosis was struma diffusa colloides et parenchymatosa basedowiana.

The tests showed:

Iodine content, 0.480 per cent of dry substance.
Effect on the tadpoles, very strong (no. 5 in fig. 11).
Effect on rat, not determined.

CASE 7.—B. M., a housewife, aged 36, lived in Austria ("near Tyrol") up to the age of 19, and since then in California, on the coast. She had symptoms of Basedow's disease fourteen years before the operation, but she was better without medical treatment. The symptoms developed again ten months before operation, with nervousness, palpitation, tremor, excessive perspiration, tachycardia, increased appetite, muscular weakness and loss of weight (18 pounds [8.2 Kg.] in six months). The patient was treated with compound solution of iodine (10 drops three times a day) for three weeks preceding the operation. The

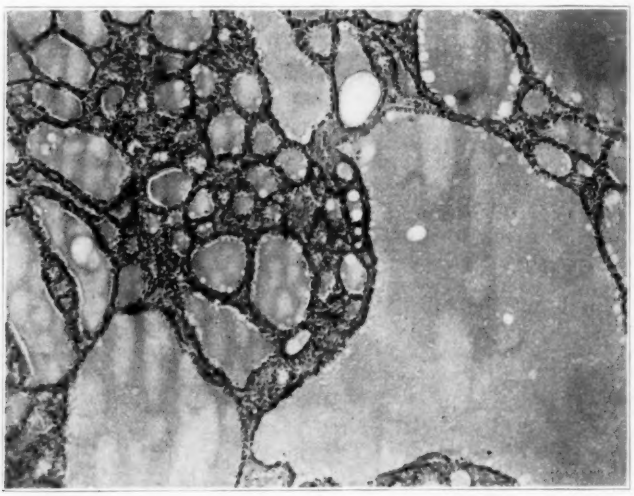


Fig. 9 (case 19).—Struma nodosa colloides macrofollicularis, clinically indifferent. Van Gieson; × 75.

basal metabolic rate was 51 per cent plus before the administration of iodine and it dropped to 36 per cent plus after sixteen days of treatment. The other symptoms improved accordingly.

The removed tissue weighed 47 Gm., and consisted of two pieces 8 by 4 by 2.5 cm. and 5.5 by 2.5 by 1 cm.

Microscopic examination of the specimen showed that the follicles were mostly small with faint to medium staining colloid and chiefly cuboidal epithelium. Some follicles were of medium to fairly large size with flat epithelium. Areas of heavy lymphocytic infiltration were numerous.

The histologic diagnosis was struma diffusa basedowiana.

The tests showed:

Iodine content, 0.246 per cent of dry substance.
Effect on the tadpoles, medium (no. 7 in fig. 11).
Effect on rat, + 108 mm. of mercury.

CASE 9.—G. F., a housewife, aged 46, always lived in California (bay region). The first symptoms of Basedow's disease developed four years before the operation. The patient felt improved after a vacation and felt well for one year. Two years before the operation, the symptoms again developed and became much worse after an attack of influenza eight months before. They were typical but of a moderate degree, consisting of nervousness, palpitation, tachycardia and loss of weight (16 pounds [7.3 Kg.]). The basal metabolic rate was 52 per cent plus three months before the operation. The patient was treated from then until the time of the operation with compound solution of iodine (3 drops three times a day) and felt much improved. She gained 5 pounds (2.3 Kg.), and the tremor and the hyperhidrosis especially were less severe. There was no exophthalmos at the time of the operation.

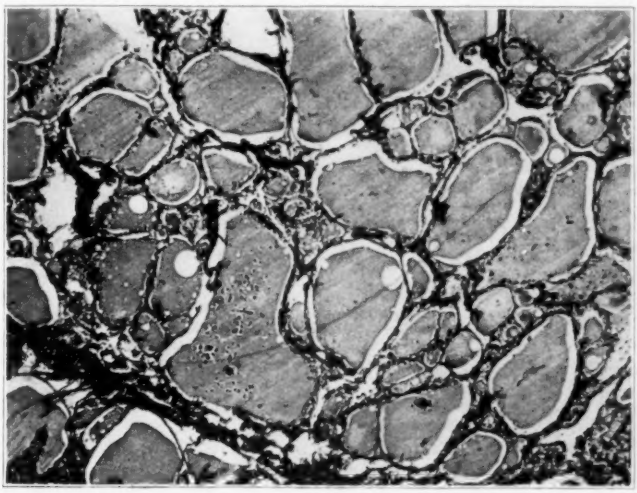


Fig. 10 (case 34).—Struma nodosa colloides macrofollicularis, clinically with hyperfunction. Van Gieson; × 75.

The removed tissue weighed 45 Gm., and consisted of three pieces, 6 by 4 by 2, 4 by 2 by 1 and 3.5 by 1.5 by 1 cm.

Microscopic examination of the specimen showed large follicles with flat epithelium and deeply staining colloid. In other parts sections with small follicles, lined by tall columnar epithelium, partly desquamating, were seen. Small infiltrations of lymphocytes were numerous in these parts.

The histologic diagnosis was struma diffusa basedowiana (fig. 3).

The tests showed:

Iodine content, 0.560 per cent of dry substance.

Effect on the tadpoles, very strong (no. 9 in fig. 11; fig. 4).

Effect on the rat, + 161 mm. of mercury.

CASE 11.—B. N., an unmarried woman, aged 45, always lived in California (bay region). She knew of her goiter only one month before the operation. The symptoms were typical, but not severe, and consisted of nervousness, palpitation,

tremor, loss of weight and increased appetite. No exophthalmos was present. Treatment with iodine was not reported.

The removed tissue weighed 27 Gm., 7.5 by 3 by 1.8 and 4.5 by 3 by 1 cm.

Microscopic examination showed the follicles to be predominantly small, with pale to medium staining colloid and lined by tall cuboidal epithelium, which was desquamated in many follicles. Infiltrations of lymphocytes were frequent.

The histologic diagnosis was struma diffusa parenchymatosa basedowiana.

The tests showed:

Iodine content, 0.029 per cent of dry substance.
Effect on the tadpoles, slight (no. 11 in fig. 11).
Effect on the rat, not determined.

CASE 13.—A. A., a housewife and teacher, aged 33, lived in different parts of Canada, and for the last three years in California (Lake Tahoe region). She was nervous during the last seven years. The cardinal symptoms developed after salpingectomy and appendectomy sixteen months before the operation for goiter and became more severe after ten months. The symptoms were typical, consisting of nervousness, tachycardia, palpitation, hyperhidrosis, increased appetite, diarrhea, muscular weakness and exophthalmos. Graefe, Stellwag, Moebius' signs were positive. Treatment with compound solution of iodine (0.6 cc. three times a day) was administered two and one-half weeks before the operation.

The removed tissue weighed 30 Gm., and consisted of two pieces measuring 4.5 by 3 by 1.6 and 5.5 by 2.5 by 2 cm.

Microscopic examination of the specimen showed that the follicles were small to medium in size, with medium stained colloid which showed serrated edges in some instances. The epithelium was high columnar, in many follicles in two and three layers. Collections of lymphocytes were infrequent.

The histologic diagnosis was struma diffusa parenchymatosa basedowiana.

The tests showed:

Iodine content, 0.228 per cent of dry substance.
Effect on tadpoles, medium (no. 13 in fig. 11).
Effffect on the rat, not determined.

CASE 14.—B. V., a housewife, aged 25, lived in California (central plain) all her life. Symptoms of goiter began one and one-half years before the operation. She was treated with compound solution of iodine on alternate weeks, some months before operation. She felt relieved at first, but four months before the operation, after she had discontinued taking iodine for a while, she became worse. She did not take any iodine until nine days before the operation (0.6 cc. three times a day) at which time the basal metabolic rate was 61.4 per cent plus. The symptoms were typical, consisting of nervousness, tremor, hyperhidrosis, tachycardia, increased appetite, loss of weight (15 pounds [6.8 Kg.] during the last two months). Exophthalmos was marked. Graefe, Stellwag and Moebius' signs were positive.

The removed tissue weighed 27.5 Gm., and consisted of two pieces 5 by 3 by 2.5 and 5 by 3 by 2 cm.

Microscopic examination showed a "classic picture." There were rather uniformly small follicles with little or no colloid. The colloid was faintly stained and vacuolated. The epithelium was tall columnar, partly desquamated, forming papillae in many follicles. Small areas of lymphocytes were present. There was no sign of involution.

The histologic diagnosis was struma diffusa parenchymatosa basedowiana (fig. 5).

The tests showed:

Iodine content, 0.196 per cent of dry substance.
Effect on the tadpoles, slight (no. 14 in fig. 11; fig. 6).
Effect on the rat, not determined.

CASE 29.—T. A., a girl, aged 14, lived in northern California until the age of 9, and in the bay region ever since. She had had goiter and symptoms for two years. She was treated intermittently with iodine (amount not known), which relieved the symptoms temporarily but they became worse when the treatment was discontinued. During the last few months preceding the operation, the illness became more severe. When the patient entered the hospital she showed the typical picture of exophthalmic goiter: nervousness, palpitation, tremor, tachycardia (from 100 to 120), loss of weight and increased appetite. Exophthalmos was present, and the Stellwag, Graefe, Moebius' signs were positive. The basal metabolic rate was 80.8 per cent plus (Benedict-Talbot) or 81.5 per cent plus (Benedict-Hendry-Baker). The patient was treated with compound solution of iodine (0.6 cc. three times a day) three weeks before the operation, under which treatment she improved.

The removed tissue weighed 106 Gm., and consisted of two pieces, measuring 7.5 by 5 by 3 and 8 by 4 by 4 cm.

Microscopic examination of the specimen showed many medium to large follicles, filled with pale to medium staining colloid and lined by flat to low cuboidal epithelium, proliferating in places. The colloid was vacuolated in many follicles. Areas with very small follicles and tall columnar epithelium, forming papillae, were present. Here the follicles were empty or filled with little pale colloid. Lymphoid tissue in the form of small follicles to large infiltrations was abundant. There was no increase of fibrous tissue.

The histologic diagnosis was struma diffusa basedowiana.

The tests showed:

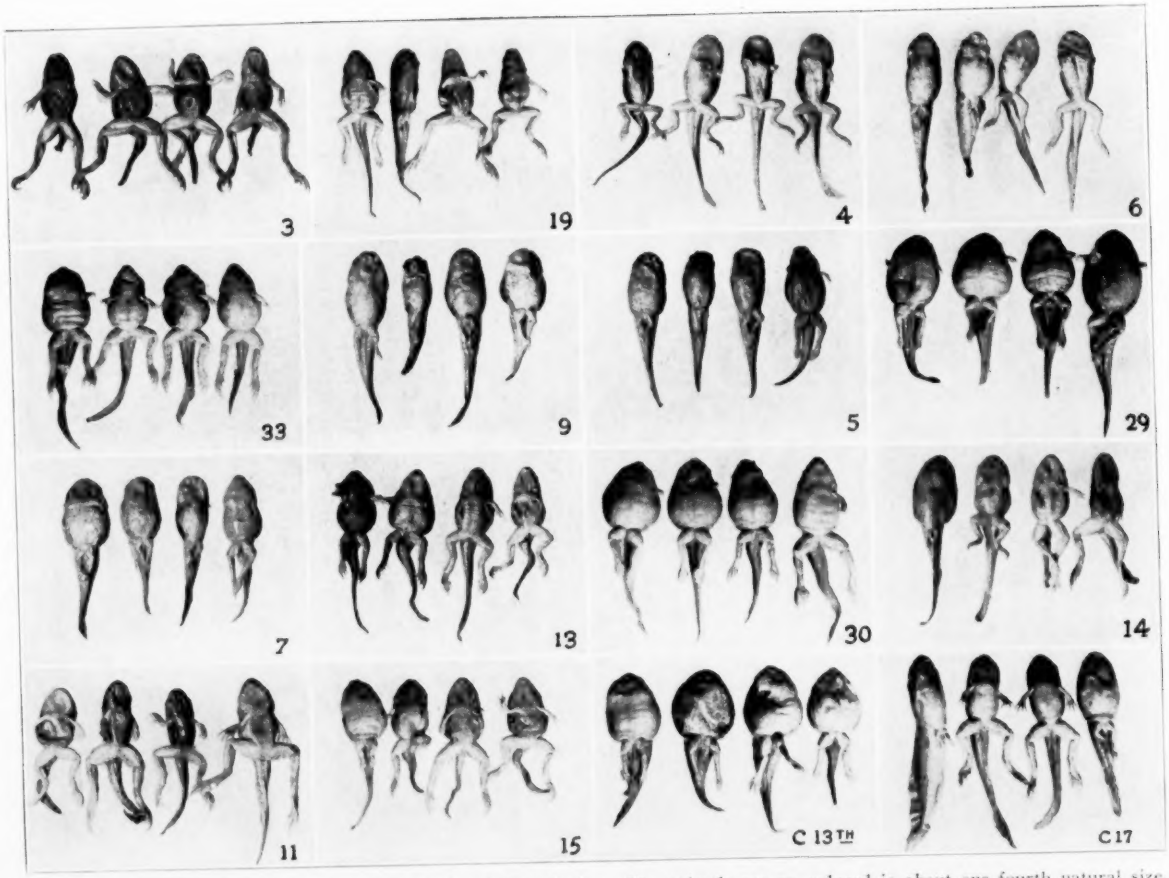
Iodine content, 0.318 per cent of dry substance.
Effect on the tadpoles, very strong (no. 29 in fig. 11).
Effect on the rat, + 115 mm. of mercury.

CASE 30.—H. E., a married woman, aged 42, lived in Montana and Idaho 0-25, then on the Pacific coast and for the last year in the bay region. She had symptoms of hyperthyroidism for one year, and a definite goiter for from three to four months. The symptoms were typical and severe, consisting of nervousness, palpitation, excessive perspiration, tachycardia (from 100 to 110), increased appetite and loss of weight (20 pounds ([9 Kg.] in six months). No exophthalmos was present. The patient was treated with compound solution of iodine (0.6 cc. three times a day) for one month before operation.

The removed tissue weighed 60 Gm., and consisted of two pieces measuring 6 by 4 by 2.5 and 5 by 3.5 by 2 cm.

Microscopic examination showed the great majority of the follicles to be medium to large in size, with scant colloid in general, and flat epithelium. In some follicles the epithelium proliferated and was cuboidal to columnar. Throughout the sections were areas with small follicles with no or little colloid, lined by tall columnar epithelium. Small collections of lymphocytes were present.

The histologic diagnosis was struma diffusa basedowiana.



Figs. 11 and 12.—Effect on the metamorphosis of the tadpoles. The animals are reproduced in about one fourth natural size. C4, C8 and C17 are normal controls, fed liver and lettuce. C5th and C13th are controls fed with thyroid tablets (Burroughs and Wellcome). The other figures are the numbers of the cases. The animals of case 1 and 2 and of eleven controls have not been represented.

Figs. 11 and 12.—Effect on the metamorphosis of the tadpoles. The animals are reproduced in about one fourth natural size. C4, C8 and C17 are normal controls, fed liver and lettuce. C5th and C13th are controls fed with thyroid tablets (Burroughs and Wellcome). The other figures are the numbers of the cases. The animals of case 1 and 2 and of eleven controls have not been reproduced.

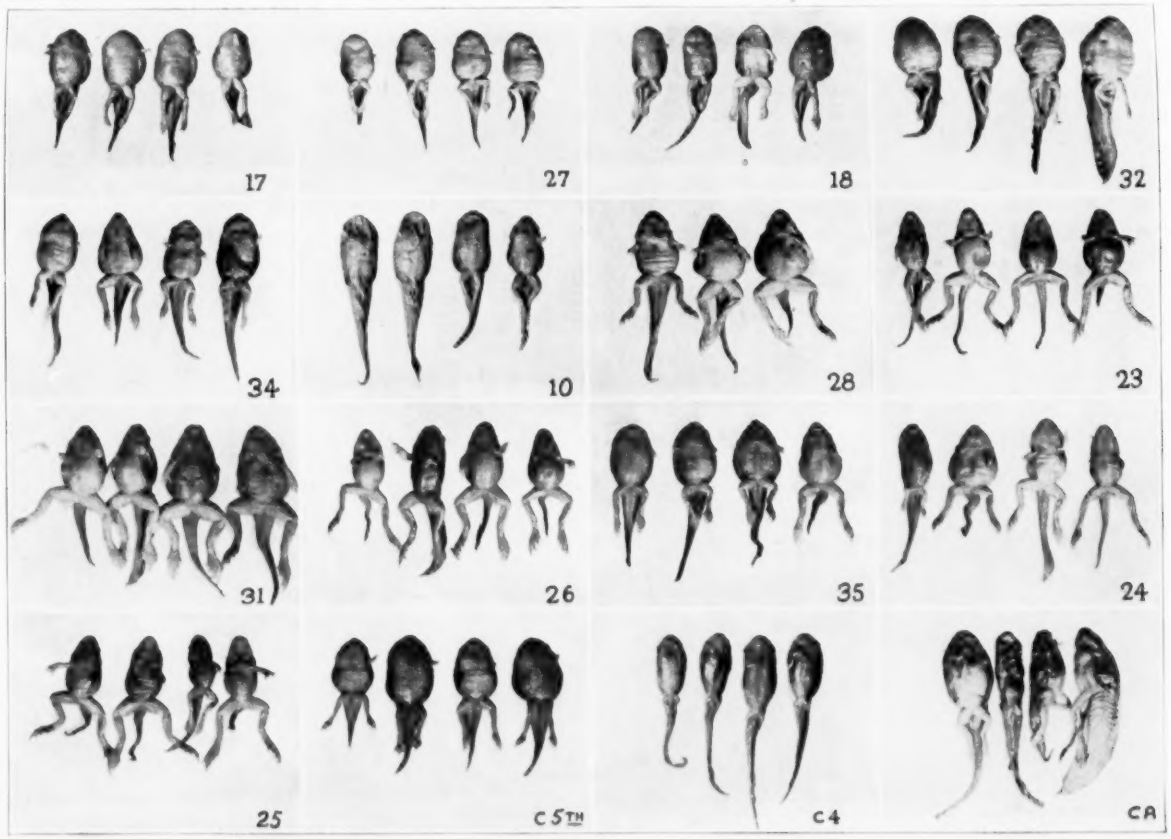


Fig. 12.

Case	Iodine Content, per Cent (Dry Substance)	Clinical Symptoms	Effect on Tadpoles (Average Time of Death in Days) (1) Experimental Tadpole	(2) Control	(3) Difference 1–2	Effect on Rat, Mm. of Hg	Colloid Content (Estimated)	Histologic Diagnosis	Duration of Goiter, Years	Duration of Symptoms, Years	Age of Patient	Use of Iodine
						I. Goiter with Hypofunction						
33	0.148	Hypofunction; basal metabolic rate, 19% superimposed by hyperfunction ?	32¼	19	+13¼	+38	+++	Struma diffusa colloides et nodosa colloides nonproliferans	?	?	33	
						II. Adenomas, Clinically Indifferent						
6	0.0323	Indifferent	Killed after 90	13	(77)*	....	0 to +	Struma nodosa macrofollicularis proliferans et nonproliferans et nodosa parenchymatosa microfollicularis	11	?	19	
4	0.0344	Indifferent	Killed after 90	13	(77)	....	+ to ++	Struma nodosa macrofollicularis nonproliferans et nodosa parenchymatosa microfollicularis	12	..	43	
19	0.0372	Indifferent	60	15	45	+50	+++	Struma nodosa macrofollicularis proliferans et nonproliferans	25	..	49	
3	0.0390	Indifferent	55½	12	43½	+60	0	Struma nodosa parenchymatosa partim trabecularis	More than 5	..	58	Yes; amount and time used not known
25	0.0411	Indifferent	60	15	45	....	+ to +++	Struma nodosa colloides macrofollicularis nonproliferans et nodosa parenchymatosa microfollicularis	25	..	55	
24	0.0501	Indifferent	34¾	15	19¾	+89	+++	Struma nodosa colloides macrofollicularis partim proliferans	5	..	68	
35	0.193	Indifferent	23	19	+ 4	....	+++	Normal gland with a few nodules (struma nodosa colloides macrofollicularis nonprolifrans)	?	..	42	
Controls†	0.4	.....	.... 12, 13, 15, 19			+171						
						III. Adenomas with Slight or Questionable Hyperfunction						
31	0.0605	Mild or questionable; basal metabolic rate, +4.5%	54¾	15	+39¾	....	0 to +	Struma nodosa parenchymatosa microfollicularis	18	6 mo.	40	
26	0.0672	Mild	55½	15	+40½	....	+ to ++	Struma nodosa colloides macrofollicular (partim basedowificata) et nodosa parenchymatosa microfollicularis	20	3	67	
28	0.0675	Slight hyperfunction ?	41	15	+26	....	+ to +++	Struma nodosa colloides macrofollicularis proliferans et nodosa parenchymatosa microfollicularis	2	6 mo.	34	Probable 2 years ago
23	0.0980	Mild	42	15	+27	....	± to ++	Struma nodosa colloides macrofollicularis proliferans et parenchymatosa microfollicularis				

						IV. Adenomas with Definite Hyperfunction						
10	0.147	Moderate	17	13	+ 4	+ 98	+++	Struma nodosa colloides basedowificata	20	2	49	Probable 5 months ago
18	0.163	Severe	13	15	— 2	+124	+ to +++	Struma nodosa colloides basedowificata	Not known	2	61	
34	0.204	Moderate to severe; basal metabolic rate, +20.4%	29¾	19	+ 1¾	+109	+++	Struma nodosa colloides macrofollicularis partim proliferans	18	2	40	
32	0.232	Moderate	16¾	15	+ 1¾	....	++++	Struma nodosa colloides macrofollicularis proliferans	18	3	33	
17	0.249	Very severe	11	15	— 4	+174	+ to +++	Struma nodosa colloides basedowificata	18	6	62	
27	0.276	Severe	13	15	— 2	+149	+ to +++	Struma nodosa colloides basedowificata et nodosa parenchymatosa microfollicularis	16	1	55	Ten drops three times a day during 3 months
Control†	0.4	.....	....	13, 15, 19	....	+171						
						V. Struma Diffusa Basedowiana						
11	0.0290	Mild	(52)‡	15	(+37)	.....	+	Struma diffusa parenchymatosa basedowiana	1 mo.? 1½	1 mo.? 1½	45 25	None 0.6 cc. three times a day for 9 days
14	0.196	Severe; basal metabolic rate, +61.4%	40	15	+25	.....	0 to +	Struma diffusa parenchymatosa basedowiana	3-4 mo.	1	42	0.6 cc. three times a day for 1 month
30	0.208	Severe	26	15	+11	+105	++	Struma diffusa basedowiana.....	16 mo.	10 mo.	33	0.6 cc. three times a day for 2½ weeks
13	0.228	Moderate	25	15	+10	.....	+ to ++	Struma diffusa parenchymatosa basedowiana	?	10 mo.	36	10 drops three times a day for 3 weeks
7	0.246	Moderate; basal metabolic rate, +51.0%	19	13	+ 6	+120	+ to ++	Struma diffusa basedowiana.....	2	2	14	0.6 cc. three times a day for 3 weeks
29	0.318	Severe; basal metabolic rate, +81.5%	17¾	15	+ 2¾	+115	++	Struma diffusa basedowiana.....	?	6 mo.	48	10 drops three times a day for 3 weeks
5	0.480	Moderate	15	13	+ 2	.....	++ to +++	Struma diffusa basedowiana.....	2	2	46	3 drops three times a day for 3 months
9	0.560	Moderate; basal metabolic rate, +52%	14	13	+ 1	+161	+++	Struma diffusa basedowiana.....	..	..	29	
Controls†	0.4	.....	....	13, 15	....	+171						

* Figures in parentheses indicate incomplete observations.
† Thyroid gland, Burroughs and Wellcome.
‡ Was fed for thirty-six days only, but showed the lowest effect of the whole series.

The tests showed:

Iodine content, 0.208 per cent of dry substance.
Effect on the tadpoles, strong (no. 30 in fig. 11).
Effect on the rat, + 115 mm. of mercury.

THE IODINE CONTENT

The two extremes found in this group were 0.029 and 0.56 per cent. The average iodine content of the goiters of seven patients treated with compound solution of iodine was the highest of all the groups, 0.3194 per cent. The goiter of the only untreated patient showed an iodine content considerably below normal. Both results are in agreement with the findings of a number of other authors (Branovačky,[24] Holst and Lunde[25]). Branovačky, for instance, gave as an average for untreated severe cases 0.0547 per cent and for mild cases, 0.0223 per cent.

A certain relationship exists between the iodine content and the quantity of iodine administered before operation, as the patient with the highest percentage was treated for three months and the one with the lowest for only nine days. But between these two extremes there exists no correlation whatsoever. The patients in cases 5 and 7 were both treated with the same amount, and the percentages were 0.246 and 0.480.

THE COLLOID CONTENT

Section V of the table shows clearly that the colloid content is parallel to the iodine content, confirming the well known fact that treatment with iodine increases the colloid content, described by A. Kocher, Cattell,[26] and later especially by Rienhoff.[27] Recently, however, some authors, particularly Hellwig,[28] pointed out that the high colloid content too often is attributed to the preoperative treatment with iodine. He claimed that goiters of Graves' disease with rich colloid but with flat epithelium are not "lugolized hyperplasia" but diffuse colloid goiters with beginning "basedowification" and that these can always be distinguished from goiters in which the colloid content increased as a result of treatment with iodine by the taller epithelium

24. Branovačky (footnotes 4 and 9).

25. Holst, J., and Lunde, G.: Intermediate Iodine Metabolism During the Preoperative Treatment of Exophthalmic Goitre, Am. J. Surg. **7**:39, 1929.

26. Cattell, R.: The Pathology of Exophthalmic Goitre, Boston M. & S. J. **192**:989, 1925.

27. Rienhoff, W. F.: Histologic Changes Brought About in Cases of Exophthalmic Goitre by Administration of Iodine, Bull. Johns Hopkins Hosp. **37**:285, 1925.

28. Hellwig, C. A.: Form und Funktion des nordamerikanischen Kropfes, Arch. f. klin. Chir. **154**:1, 1929.

in the large follicles. I agree that the diagnosis of "lugolized hyperplasia" is made too often. As a rule, a consideration of the patient's history will decide.

The biologic activity showed a complete dependence on the iodine and colloid content in this group. However, it is to be said that slight deviations might have been found in a greater number of cases. The biologic activity, as already mentioned, was lower than in the adenomas with hyperfunction, although they were clinically more active and the iodine content was higher. The fact that adenomas are much less vascularized than the diffuse gland and that they are devoid of lymph vessels might suggest that their higher biologic activity is due to incomplete resorption of the active substances. None of the goiters was more active than the thyroid tablets of Burroughs and Wellcome.

Section V of the table also shows that in this group there is no relationship whatsoever between the clinical and the biologic activity. The two extremes, the goiter in cases 14 and 9, are of special interest. The goiter in case 14 was clinically very severe, with a basal metabolic rate of plus 61.4 per cent after three days of treatment with iodine, and the goiter showed the old classic picture of the struma diffusa parenchymatosa basedowiana with little or no colloid (fig. 5). The biologic activity was very slight, as figure 6 demonstrates. It was even lower than in case 24, a clinically indifferent struma nodosa colloides. The biologic activity of the goiter in case 11, in which the patient had not been treated with iodine, was even less active. Unfortunately the tests on rats could not be made in these cases.

On the other hand, the goiter in case 9, which showed a moderate clinical hyperfunction (basal metabolic rate + 52 per cent before the treatment with iodine), was very active in both tests (fig. 4). Wegelin and Abelin [29] and Branovačky [4] each reported one case of goiter with the typical picture of the struma diffusa parenchymatosa basedowiana which failed to induce or showed only a very slight effect on the metamorphosis of the tadpoles. The goiter in the case of Wegelin and Abelin showed only traces of iodine; in the case of Branovačky, it was richer in iodine. Preoperative treatment with iodine is not probable in either of these cases.

The study of Williamson, Pearse and Cunnington [11] revealed the same fact on a greater number of goiters. Nine specimens of struma diffusa parenchymatosa with little or no colloid, which had not been treated with iodine before the operation, failed to induce metamorphosis. Six of these goiters contained no iodine (determined with the method of von Fellenberg) and three very little (0.008, 0.009

29. Wegelin and Abelin (footnote 2, second reference).

and 0.064 per cent). Furthermore, 500 Gm. of moist material of the same untreated type was digested after the method of Harrington, and the digest was precipitated with acid. The precipitate, which contained 1.04 per cent iodine, was neutralized and fed to tadpoles without accelerating the metamorphosis. Iodine-treated, colloid-containing goiters of Graves' disease were not tested.

It would lead too far to discuss the theory these authors developed from their findings. But they show, together with Wegelin and Abelin, Branovačky and my findings, that untreated or insufficiently treated, but clinically very active, glands of Graves' disease can have little or no effect in the Gudernatsch test. On the other hand, there are cases reported in which the goiters had a very low iodine and colloid content and which were biologically very active. For instance, the goiter in a case of Wegelin and Abelin (1921) with 0.011 per cent iodine content was at least as active as the thyroid tablets (Burroughs and Wellcome) and therefore as active as the goiter in case 9 of my series with 0.560 per cent iodine, and with the highest biologic activity, about fifty times higher.

How are these facts to be explained? Recent investigations on the iodine metabolism show the action of the iodine on patients with primary exophthalmic goiter. Von Fellenberg,[30] and Veil and Sturm[31] showed that in cases of primary thyrotoxicosis the iodine content of the blood is always increased. Holst and Lunde[25] confirmed these findings, and furthermore, by separating the blood iodine by von Fellenberg's method into the alcohol-soluble inorganic and the alcohol-insoluble organic fraction, demonstrated that not only the percentage of the total but also the percentage of the organic blood iodine is greatly increased in patients with primary exophthalmic goiter. According to these authors, the figures for the inorganic fraction are considerably heightened during the administration of iodine, while the organic fraction "is reduced to the normal or almost to the normal figures and the fall is practically parallel to the decrease of the metabolism figures." At the same time, as is well known, a retention of the colloid and iodine in the goiter occurs. These investigations therefore would suggest that the effect of the administration of iodine can be explained merely by the law of mass action, thus confirming the view of different clinicians who called it drastically a "constipation" of the gland. It is, however, hardly conceivable that there should not be enough thyroxin (and other active substances) left in a gland which is still so active as to maintain a high basal metabolism to induce metamorphosis.

30. von Fellenberg, T.: Das Vorkommen, der Kreislauf und der Stoffwechsel des Jods, Ergebn. d. Physiol. **25**:176, 1926.

31. Veil, W. H., and Sturm, A.: Deutsches Arch. f. klin. Med. **147**:166, 1925.

Romeis[32] showed that a solution of thyroxin 1:100,000,000 is still definitely active. Therefore, the theory of Plummer,[33] and of other authors, that in advanced stages of primary exophthalmic goiter the gland produces an abnormal, incompletely iodized thyroxin, would gain support, assuming, however, that this abnormal thyroxin, probably together with other substances, would only act on the metabolism but not on the metamorphosis. Swingle[34] showed that acetyl-thyroxin induces metamorphosis in tadpoles but does not act on the metabolism. The same authors' point of view, that the gland is exhausted sooner in one patient and later in another, would explain the fact that goiters with little iodine and colloid are active in the Gudnernatsch test in the one case and inactive in the other.

It is difficult to decide, from the work of the earlier workers and from the experiments reported here, whether the struma diffusa parenchymatosa basedowiana is brought back to normal in its biochemistry and in its function by treatment with iodine, a view held by Marine[13] and other authors. It is a well established fact that the struma basedowiana is more active (with certain exceptions mentioned before) than the clinically indifferent diffuse colloid goiter, both in the Gudernatsch and in the Asher-Streuli test. But unfortunately, only a few normal glands have been subjected to these tests. Wegelin and Abelin[35] have two normal glands in their series which were both as active as the thyroid tablets of Burroughs and Wellcome but the same was true of the only untreated struma basedowiana. Branovačky[4] found that two normal glands were on the average slightly less active than the strumae basedowianae which probably had not been treated with iodine. In the series reported here three iodine-treated strumae diffusae basedowianae were decidedly more active than the specimen in case 35 which consisted mainly of normal thyroid tissue. Three others were only little less active. This would therefore suggest that under the treatment with iodine in certain cases the potency of the gland is actually not decreased but increased. Only investigations on a larger scale, including biologic tests, will be able to solve this problem.

COMMENT

The reported findings show that the correlation between the iodine and colloid content, and between the iodine content and the biologic

32. Romeis, B.: Biologische Versuche ueber die Wirksamkeit verschiedener Thyreoideapraeparate, Ztschr. f. d. ges. exper. Med. **4**:379, 1916; **5**:99, 1917; **6**:101, 1918.

33. Plummer, H. S., and Boothby, W. M.: The Value of Iodine in Exophthalmic Goitre, J. Iowa State M. Soc. **14**:66, 1924; footnote 21.

34. Swingle: Am. J. Physiol. **70**:208, 1924.

35. Wegelin and Abelin (footnote 2, first reference).

activity, of adenomas in California is not so great as in the material in Cleveland (Marine [13]) but is greater than in the material in Bern (C. Abelin [3]) and in Munich (Spatz,[10]). The extremes in a given group generally follow the rule that those with the higher iodine content are richer in colloid and are biologically more active than those with low iodine content. The deviating results might be due, as Spatz [10] suggested, to the more widespread use of iodine in areas of endemic goiter.

The relationship between the iodine content and the clinical activity of adenomas seems to be much closer, in agreement with the reports of Wegelin and Abelin,[2] Branovačky [24] and Spatz.[10] The iodine content increases from the low figures of the clinically indifferent cases through the clinically slight to the clinically severe hyperactive adenomas.

The comparison of the iodine content and the biologic activity of adenomas in California, an area on the periphery of an endemic, with those found in centers of endemics is of special interest. The iodine content of clinically indifferent adenomas of different histologic structure ranged within the same limits, as the one in Freiburg (Germany), Munich (Germany), Bern (Switzerland) and Cleveland (Ohio). However, low figures as in Bern and Cleveland were not found. The group of clinically hyperactive adenomas showed a considerably higher iodine content than all the adenomas in the localities mentioned before.

The biologic activity of clinically indifferent adenomas was about the same as in Bern and in Munich, to judge from the comparison with the effect of standardized thyroid substances. On the other hand, the biologic activities of the adenomas with hyperfunction was higher than the one of all the types of goiters in Bern. This fact might be attributed to the higher iodine content. It is impossible to compare the results with those in the other regions of endemic goiter, since no standard effect was determined there.

The relationship between the iodine content and the biologic activity, as compared with the action of thyroid tablets of Burroughs and Wellcome, is of great interest. Three clinically very active adenomas with an iodine content of 0.163 to 0.276 per cent were biologically more active than the thyroid tablets with 0.4 per cent (fig. 7), whereas two strumae diffusae basedowianae with a higher iodine content (0.560 and 0.480 per cent) were slightly less active; and one of this series with 0.560 per cent was approximately as active as one of Wegelin and Abelin's [35] with 0.011 per cent.

It is evident that in the iodine-treated goiters of primary Graves' disease not all the iodine is present in an active form. One must assume the same for the normal thyroid substance, if one does not

accept the point of view that in the adenomas with hyperfunction the iodine occurs in a more active form. All these considerations lead to the conclusion that not the quantity but the quality of the iodine compounds determine the biologic and clinical activity of normal and goitrous glands.[36]

Different facts clearly indicate that the adenomas with hyperfunction differ biologically from the diffuse goiters of primary Basedow's disease. The relation between the iodine content and the clinical activity is rather constant in adenomas, but is entirely missing in the iodine-treated struma basedowiana, in which the biologic activity is parallel to the iodine content. The biologic activity of the latter is high when under the successful treatment with iodine the symptoms of hyperthyroidism have partly subsided. No instance of a clinically hyperactive but biologically inactive adenoma has even been reported, as in the case of struma diffusa basedowiana.[37] All these differences greatly support the view of Plummer [21] and others that a fundamental difference exists between the two forms of hyperthyroidism.

A dysfunction of the various types of goiter seems at the present time the most discussed problem. It was advocated for the struma basedowiana by Moebius and is today supported especially by Plummer [21] and by de Quervain.[18] The results of the experiments reported here together with those of other authors seem to substantiate their view. Wegelin and Abelin [20] demonstrated a dysfunction of different types of goiters in their experiments on tadpoles. The same was found in two adenomas of this series. Furthermore, the deviation of the results of the two biologic tests suggests the existence of a secretion changed in its quality, but not in the same manner as in the adenomas and in the goiters of Graves' disease. No results as to the nature of these different forms of dysfunction have been brought forward in this investigation.

36. Harington and Randall (The Chemical Assay of Thyroid Gland, Quart. J. Pharm. & Pharmacol. **2**:501, 1929) showed that the thyroxin-iodine varies between 28 and 60 per cent of the total iodine.

37. It is impossible, from these experiments, to decide whether this is due to morphologic factors (lower degree of resorption) or to the biologic properties of the products of secretion.

GRANULOPENIA (GRANULOCYTOPENIA)

WITH SPECIAL REFERENCE TO CLASSIFICATION AND BENIGN TYPES *

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The syndrome first described by Schultz [1] as agranulocytosis was considered by him to represent a definite clinical entity. Other observers who also held this view based their opinions on the fairly uniform clinical history, particularly the age and sex predilection and the peculiarity in the distribution of the supposedly specific lesions. However, subsequent contributions have indicated that a similar hematologic picture occurs with varying clinical features and apparently is based on a variety of causes. Later observations have strengthened the view that the disease is symptomatic of a number of etiologic factors, such as infection, chemical agents and the action of x-rays and radium. The protagonists of the theory that the disease is a distinct entity believe: (1) that it represents a specific primary disease or infection of the granulopoietic structure in the bone marrow with the necrotic lesions in the mouth as an expression (Schultz), or (2) that the lesions in the mouth form the primary focus of a specific infection. The opponents of this conception agree that there is an abnormal response to the various types of infection or chemical poisons with diminution or disappearance of the granulocytes; they believe that this defect is probably due to differences in distribution or to actual injury of the granulopoietic mechanism, with destruction or lack of production in these cells. An attitude of compromise is taken by Dahlen and Wahlgren,[2] who believe that the condition is the result of infection acting on a predisposition in the form of hypoplasia of the myeloid structures. These conflicting views not only have created a controversial aspect in the discussion of granulopenia, but have indicated the necessity for a more precise terminology and a more careful subdivision of these various

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* From the Graduate School of Medicine, University of Pennsylvania, and the Laboratories of the Jewish Hospital.

1. Schultz, W.: Deutsche med. Wchnschr. **48**:1495, 1922.

2. Dahlen, B., and Wahlgren, F.: Acta med. Scandinav. **65**:407, 1926.

groups. Not the least important is the removal of the equivocal designation of agranulocytosis. Among the earliest authors to prefer the term granulocytopenia was David.[3] Based on analogy with such terms as "leukopenia" and "thrombopenia," we see no objection to the abbreviated term of granulopenia, which has been adopted recently by Roberts and Kracke.[4]

We believe that the syndrome described by Schultz merits the term of primary granulopenia, and that instances without discoverable cause and corresponding to his original description should properly fit into this category. This premise would rest on a sounder basis if it were possible to lay down certain criteria in the same manner in which one now distinguishes pernicious anemia from secondary anemia. The term secondary granulopenia seems appropriate for the larger group of cases due to known causes. A satisfactory classification not dissimilar to the one recently advocated by Roberts and Kracke is as follows:

Primary Granulopenia	*Secondary Granulopenia*
(a) Acute (Schultz)	(a) General infections
(b) Chronic (recurrent)	Influenza
	Typhoid
	Some exanthemasa
	Sepsis, etc.
	(b) Focal infection
	(c) Chemical (arsphenamine, benzene)
	(d) Irradiation (x-rays, radium)
	(e) Blood diseases (leukemia, splenic diseases, aplastic anemia, etc.

PRIMARY GRANULOPENIA

The characteristic clinical features of primary granulopenia or agranulocytosis of Schultz, Friedemann [5] and others have been described so frequently that it suffices here to review briefly the salient features. In a typical case, an acute febrile illness occurs in a middle-aged woman, with prostration, usually mild jaundice, sore throat and necrotic, ulcerative or gangrenous lesions in the mouth, pharynx and vagina. Lesions in other parts of the digestive tract, such as in the esophagus, stomach, colon, rectum and anus have also been described. The leukocyte count is profoundly depressed, affecting mainly the granulocytes, with a corresponding predominance of lymphocytes. The polymorphonuclear cells may fall to lower than 10 per cent or may be entirely absent on smears. At the same time, there is little or no change in the red cells, hemoglobin or platelets. The spleen and liver are slightly enlarged. Death usually occurs within one month; in milder cases there may be recovery.

3. David, W.: Med. Klin. **20**:1614, 1924.
4. Roberts, S. R., and Kracke, R. R.: Ann. Int. Med. **5**:40 (July) 1931.
5. Friedemann, N.: Med. Klin. **19**:1357, 1923.

At necropsy, the bone marrow shows erythropoietic function, but the granulocytes are few. However, younger forms, such as myeloblasts and eosinophilic myelocytes, may be found. Myelocytes showing evidence of degeneration are also noted.

SECONDARY GRANULOPENIA

In contrast with the rather rare primary types are the relatively more common instances of depressed granulocyte counts associated with

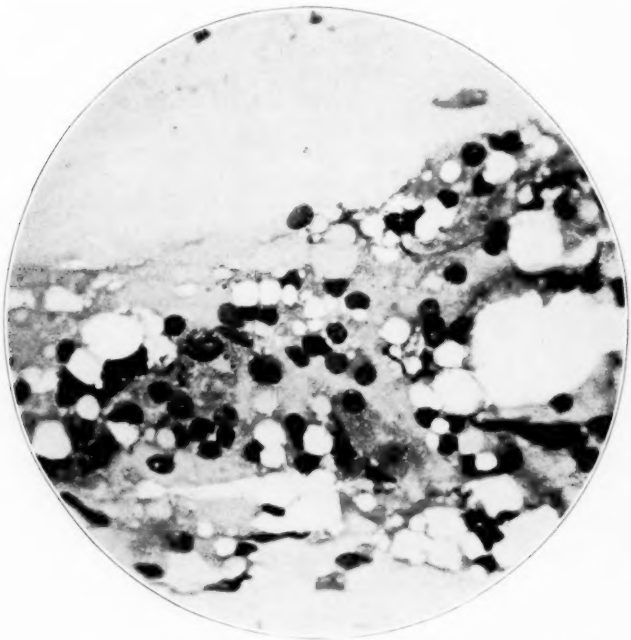

Fig. 1.—Smear from sternal marrow (postmortem) in a case of diffuse bone marrow injury following the administration of neoarsphenamine. In the center are seen a number of macroblasts (erythroblasts) with typical "cart wheel" nuclei; toward the periphery are several megaloblasts with fine vesicular nuclei. Lack of maturation of both myeloid and erythroid series is noted. No myelocytes or polymorphonuclear cells were found in any field.

general or focal infections; with conditions caused by arsphenamine, benzene and other chemical agents, or by the x-rays and radium, or with a less general aplastic state of the bone marrow, as in certain anemias. It seems more appropriate to designate such conditions as secondary types or to consider them all, as does Duke,[6] as belonging

6. Duke, W. W.: Aplastic Anemia, J. A. M. A. **91**:720 (Sept. 8) 1928.

to the general class of aplastic anemia and varying in degree or in the selective character of the aplasia. Among these types, that induced by arsphenamine has been well studied in recent years. Usually this type is associated with other signs of diffuse aplasia, such as a lowered number of red cells and platelets. Occasionally, the anemia is further increased by marked hemorrhage due to thrombopenia. It seems more likely to occur when the arsphenamine is given to a syphilitic patient who shows evidence of anemia. A typical instance observed by us was

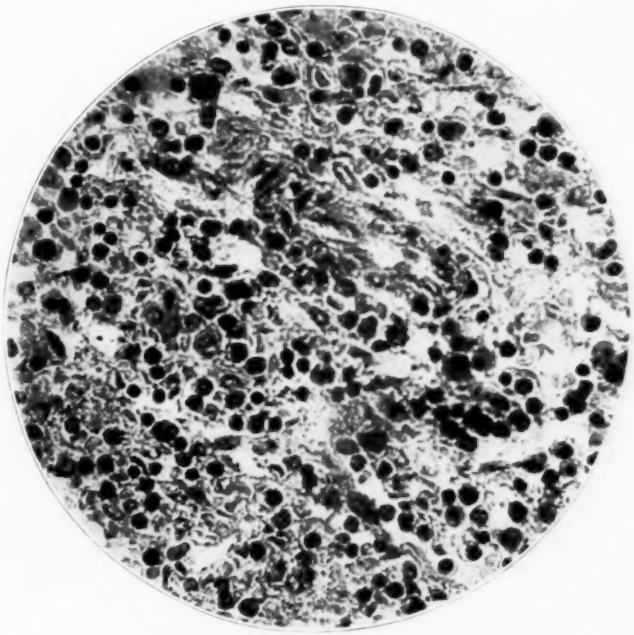

Fig. 2.—Section from marrow of femur in a patient presenting secondary granulopenia from sepsis. Normoblasts, macroblasts and megaloblasts are present, but myeloid series are represented by a few myeloblasts and degenerated myelocytes.

recently described.[7] The patient, an Italian woman, aged 45, had severe anemia and a positive Wassermann reaction. Though she was treated cautiously with small doses of neoarsphenamine, granulopenia developed, and there was a further lowering of the red cells and hemoglobin. The last leukocyte count on the day of death was 850, and neutrophils were absent in the blood smears. A series of similar instances was recently reviewed by Farley.[8] He does not believe that the arsenic in

7. Steinfield, E., and Shay, H.: M. Clin. North America **13**:923 (Jan.) 1930.

8. Farley, D.: Am. J. M. Sc. **179**:214, 1930.

the arsphenamine molecule is the cause of the phenomenon. There are several possible explanations; there may be (1) an idiosyncrasy to the arsphenamine per se, possibly creating a benzene-like action on the bone marrow or (2) a form of Herxheimer reaction with the liberation of myelotoxic substances. The latter theory appears plausible in view of the fact that in the past patients who were not syphilitic and who suffered from severe secondary anemia or pernicious anemia have at times shown improvement from the empiric use of arsphenamine.

The granulopenia secondary to irradiation is well known and has frequently been described. Granulopenia is symptomatic of various diseases of the blood and lymphatic structures. In the leukemias it appears to be due to interference with the formation of mature cells due to intense proliferation or infiltration of the leukemic cells in the bone marrow. We have occasionally seen depressed bone marrow function in carcinoma, lymphosarcoma and other malignant conditions in the absence of demonstrable invasion of the bone marrow. Whether this is due to some obscure toxic factor or to the inability of the bone marrow to cope with the demands resulting from cachexia and a disordered nutritional state, we are unable to say.

The occurrence of a granulopenic blood picture in septic states has been described in a recent article by Blumer,[9] who emphasizes the difficulty in distinguishing such cases from aplastic anemia and leukopenic stages of leukemia.

Our interest in the occurrence of moderate granulopenia associated with focal infection and ending in recovery was aroused by the following case.

CASE 1.—*History.*—B. H., a school girl, aged 7, was admitted to the Graduate Hospital, Nov. 1, 1929, with a painful swelling of the right side of the lower jaw. There was no history of familial or hereditary diseases. With the exception of measles, the previous medical history was uneventful.

Two weeks before admission, the patient had a slight sore throat. Six days before admission, the right lower molar was extracted. Following this, the jaw became swollen, and a temperature of 103 F. developed. The patient was treated in the clinic and improved, but again became worse and was admitted to the hospital.

Examination.—Physical examination on admission revealed an undernourished girl who appeared toxic; the temperature was 102 F. No icterus of the sclerae was noted. The area of the right mandible was swollen and tender. Small round white ulcers were present on the lips. The inner surface of the lower lip was covered with white plaques of oval contour with central depressions varying in size from that of a pinhead to that of a pea. A halo of reddened mucosa surrounded these areas. The right lower first molar and the second premolar were absent, and a swelling was present along the ramus of the mandible. The tonsils were reddened and cryptic but not much enlarged; no exudate was present on them. The sub-

9. Blumer, G.: Am. J. M. Sc. **179**:11, 1930.

maxillary group of cervical lymph nodes was enlarged; a soft mitral systolic murmur was present; the pulmonic second sound was accentuated. The lungs were clear. The spleen was palpable. No genital lesions were present. On admission the leukocyte count was 2,000, with the neutrophils 20 per cent, or a total of 400 cells per cubic millimeter.

Course.—After forty-eight hours the temperature began to fall, the leukocyte count had risen to 4,800, and the labial ulcerations began to heal. On November 5, there was marked general improvement, and the leukocytes had risen to 10,200, with the total number of granulocytes 27 per cent. The recovery in the number of granulocytes was preceded by a slight increase in the metamyelocyte group. The red cell and hemoglobin counts were lowest on admission, the red cells being 3,610,000, and the hemoglobin, 64 per cent; the maximum count was noted eleven days after admission, namely: 4,560,000 red cells and 71 per cent hemoglobin. Blood platelets varied from 194,000 to 230,000; the volume index was 0.78. Reticulocytes varied from 0.3 to 0.4 per cent. Cultures of the blood were sterile. The treatment, which was almost entirely local, was administered under the direction of Dr. Ivy. Though stimulating doses of roentgen irradiation for the long bones and injections of foreign protein were considered, improvement began before these measures were actually inaugurated.

The second case illustrates granulopenia associated with focal infection, occurring as part of a general aplastic blood picture.

CASE 2.—*History.*—B. E. B., a white woman, aged 40, single, was admitted to the Graduate Hospital on June 23, 1928, with the complaint of pain and swelling of the legs. The family history was not relevant. The past history was uneventful until 1918, when the patient had a nervous collapse necessitating complete rest. The present illness began in April, 1928, when the patient noticed that it was difficult to walk rapidly. It became increasingly difficult to raise the legs, and later cramplike pains were noted in the calf of the right leg. The ankles then became swollen and discolored. Pallor and general weakness appeared.

Examination.—Examination revealed a pale, undernourished, asthenic woman. No icterus was noted. Ecchymoses were present above both knees, on the anterior aspect of the thigh and in both popliteal spaces.

Hyperreflexion was present; there was no absence of vibratory sensation. Examination of the upper part of the respiratory tract made by Dr. R. H. Skillern showed hyperplastic ethmoiditis on the left side. The tonsils were buried, cryptic and badly infected, with free pus. Tonsillectomy was advised.

Dental caries were noted in the second right upper molar, and gingivitis along the gingival line of the upper right molars. A roentgenogram showed a slight infection around the second upper right molar and a broken root fragment in the region of the upper right bicuspid.

The heart was normal, with the exception of a moderate, bell-like aortic second sound. No enlargement of the liver or spleen was found; there were no palpable masses. Orthopedic examination made by Dr. W. G. Elmer showed that the right knee was pathologically flexed (20 degrees). The hamstrings were tense and contracted. Pelvic examination (made by rectum) gave normal results.

Laboratory examinations showed: blood sugar, 129 mg. and blood urea nitrogen, 10 mg. per hundred cubic centimeters. The Wassermann and Kahn reactions of the blood were negative. Fractional gastric tests showed: free hydrochloric acid present in all specimens, ranging from 5 to 35. No ova or parasites were found in stools.

Urinalysis showed a positive reaction to acid, a specific gravity of 1.017, no albumin, no sugar and no casts.

Course.—With extra nourishment and the ingestion of liver and hematinics, the blood count gradually improved. When the leukocyte count, which was 1,700 on admission, reached the satisfactory level of 7,600, tonsillectomy was done (July 31). After this, the patient gradually improved in strength and in ability to walk, though she was inhibited greatly by a listless and apprehensive attitude.

Blood platelets varied from 125,000 to 209,000. The coagulation time was seven minutes; the clot retraction, normal, and the bleeding time, two minutes.

Blood Counts in Case 2 on Various Days

Date	Hemoglobin	Red Cells	White Cells	Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes
6/28/28	36	2,000,000	1,700—	46	..	3	49	2
7/ 6/28	55	3,290,000	2,000	56	..	..	43	1
7/10/28	60	3,560,000	5,750	52	..	1	44	3
7/ 7/28	64	3,640,000	2,150	57	..	..	37	6
7/26/28	59	3,438,000	7,600	57	1	..	38	4
8/ 6/28	72	3,650,000	5,300	50	..	..	48	2
8/20/28	72	4,150,000	5,200	68	..	..	29	3

In addition to the well defined primary granulopenia of Schultz and the cases that are clearly secondary, instances are encountered that fail to fit definitely into either group, as for example that of the patient with recurring cycles of granulopenia described by Rutledge, Hansen-Prüss and Thayer.[10] Somewhat similar cases have been reported recently by Roberts and Kracke.[4]

Thompson [11] described a syndrome characterized by a febrile illness associated with leukopenia, lymphadenopathy, palpable spleen and the late appearance of white spots on the posterior part of the pharynx. The author had unusual opportunities to study some of these patients prior to the appearance of the disease. All of the seven patients who were described in this report recovered, despite the fact that in two cases cell counts showed the absence of polymorphonuclear cells. Though the condition in some of the cases also resembled infectious mononucleosis, the usual age predilection was absent.

In a series of ten patients presenting the agranulocytic syndrome described by Rosenthal,[12] there was one, a woman, aged 52, who showed a normal relative proportion between the polymorphonuclear cells and the lymphocytes, though the total leukocyte count was only 900. The author designated this case as "aleukocytic angina."

A critical survey of these somewhat atypical and borderline cases raises the question as to whether or not they may be regarded as variants

10. Rutledge, B. H.; Hansen-Prüss, O. C., and Thayer, W. S.: Bull. Johns Hopkins Hosp. **46**:369 (June) 1930.

11. Thompson, W. P.: Am. J. M. Sc. **180**:232, 1930.

12. Rosenthal, N.: New York State J. Med. **30**:695, 1930.

in the scale between the typical primary granulopenias and the secondary varieties.

There are undoubtedly many persons, otherwise normal, who exhibit a definite tendency toward granulopenia. This fact has been strikingly demonstrated by Roberts and Kracke,[4] who found from careful analysis of the blood counts of 8,000 patients that about 25 per cent show granulopenia, and that this group of persons exhibit fatigue, weakness, exhaustion and somnolence more readily and to a greater degree than those with normal granulocyte counts. In this class of granulopenic persons, they found that 56 per cent were women, the majority of whom were between 40 and 60 years of age.

Their observations are significant when considered in the light of the age period when primary granulopenia is most common. Furthermore, it is not unreasonable to suppose that this group is particularly susceptible to the obscure factor that is responsible for acute granulopenia.

EXPERIMENTAL STUDIES

With the thought of studying the mechanism of granulopenia rather than with any hope of throwing light on its etiology, we have endeavored to imitate the blood picture in this condition. For this purpose we have used inoculations of a small group of common bacteria. Rabbits were the only animals used. The following strains were selected: anhemolytic, hemolytic and green streptococci, Bacillus influenzae (Pfeiffer), pneumococcus (type I), B. coli, B. typhosus, B. proteus and Staphylococcus aureus. The inocula consisted of: (1) the bacteria in suspension; (2) Berkefeld filtrates of broth cultures; (3) supernatant fluids of cultures inactivated by cresol, U. S. P., after three days' incubation; (4) agar plus bacteria and homologous blood plus bacteria to produce infected foci in the hyperergy experiments. The first three were injected subcutaneously, intramuscularly and intravenously. The infected foci were produced in the loose tissues of the flank. In addition to the effects of simple injections, the effects of an altered state of reactivity of the experimental animal were studied with the thought that these factors may create widely different responses in individuals to the same group of organisms. This is of particular application in instances of granulopenia that are definitely associated with septic or local infections due to organisms that usually produce leukocytic response. We are mindful of the fact that emphasis has been placed on these altered states by various observers in recent years. Swift, Derick and Hitchcock[13] have studied the production of hyperergy induced by infected agar foci in an attempt to reconcile conflicting ideas of the importance of certain strains of streptococci in the production of rheumatic fever. Though it cannot be said that there exists any similarity between the attempt to produce a proliferative and exudative rheumatic lesion and the disease under discussion, there is a point of comparison between these experimentally infected foci and the focal infections occasionally associated with granulopenia. We have also studied the phenomenon[14]

13. Swift, H. F.; Derick, C. L., and Hitchcock, C. H.: Bacterial Allergy to Nonhemolytic Streptococci in Its Relation to Rheumatic Fever, J. A. M. A. **90:** 906 (March 24) 1928.

14. Arneth, J.: Die qualitative Blutlehre, Leipzig, J. A. Barth, 1920.

recently described by Shwartzman. This involves the reaction in a previously prepared site induced by the injections of bacterial filtrates into the skin of a rabbit followed by an intravenous injection of the same filtrate twenty-four hours later. The intradermal amounts are small, from 0.25 to 0.5 cc., but the intravenous doses are large, from 0.5 to 3 cc. per kilogram. In the prepared area of skin the reaction is characterized by violent hemorrhagic and necrotic reactions coming on from four to five hours after the second injection. The short incubation period distinguishes this from the well known Arthus phenomenon. Though these lesions contain polymorphonuclear leukocytes, the study of the blood during the various phases of this reaction was undertaken because of a remote resemblance to clinical cases in which necrotic lesions have suddenly appeared in the mouth within a short time after dental extractions.

In all these experiments, the blood counts were made on blood from the ear veins of the rabbits. Though the counts taken in this manner are apt to vary considerably, the results of such determinations are satisfactory if they are made under uniform conditions and with suitable precautions. Since the results of these studies will be reported in detail later, it suffices to give a brief summary of the main points.

EXPERIMENTAL RESULTS

1. The subcutaneous injections of suspensions of all the organisms used produced a leukocytosis varying in degree with the animal and with certain strains. No long-continued fall in leukocytes was induced by any of the filtrates or by the production of a state of hyperergy. With the exception of the leukopenia following intravenous injections, described later, the Schwartzman phenomenon produced no continued leukopenia.

2. Intravenous injections of inactivated cultures in broth, supernatant fluids of broth cultures, Berkefeld filtrates of typhoid cultures and, to a lesser extent, the broth mediums alone produce the following phenomenon: a sharp fall of the leukocytes to approximately one fourth of the original amount within from fifteen to fifty minutes; this affected the polymorphonuclears almost entirely; at times monocytes disappeared during the lowest counts.

At the time of the recovery of the leukocyte count, which usually began from two to four hours after the injection, stained smears showed large proportions of young forms of neutrophils and pseudo-eosinophils. In supravital preparations stained with neutral red, the return of the granulocytes was ushered in by an influx of motile forms. The bone marrow of a healthy rabbit apparently withstands this demand on granulopoiesis fairly well, in view of the observation that the same fall and recovery could be induced three or four times with several days of rest between the periods. The bone marrow of the femur was examined at the end of these observations and contained approximately the usual erythroid-myeloid ratio.

The effect of intravenous injections of peptone and like substances has been noted for a number of years. Arneth [14] fully discussed this

phenomenon in 1920. Koskowsky and Zahrzewski [15] have more recently described the changes in all the cells of the leukocyte series during peptone shock. Beard and Beard [16] have shown that the sharp fall in neutrophils initiated by peptone will also occur with intravenous injections of 1 per cent and 2.5 per cent solutions of sodium chloride. However, the leukocyte count returned to normal more rapidly than had been previously noted in experiments with peptone.

COMMENT

In the light of recent studies made by Sabin [17] and others on the physiology of bone marrow, we believe that a clearer understanding of disturbed granulocytic function is possible. From these studies it appears that granulopoiesis differs from erythropoiesis in the manner of distribution of these cells in relation to the endothelium lining the intersinusoidal capillaries of the bone marrow. Whereas the most immature of the red cells lie against the endothelium within the lumen of the vessels, the most mature of the granulocyte series (myelocyte C, metamyelocyte and leukocyte) lie outside the lumen, but against the capillary wall; the metamyelocyte and the leukocyte enter the lumen in normal circumstances. The mechanism of cell delivery involves both a vasomotor and a chemical factor. In addition, there must be present the mechanism of maturation. Therefore, leukocytosis involves both an increased delivery of cells and, if the necessity continues, the increased maturation of myelocytes, first of the older forms, and then of the younger. Sabin has considered two hypothetic factors: a chemotactic factor, *C*, and a maturation factor, *M*. The same author has also demonstrated an approximately hourly rhythm in the number of white cells, with rises in the afternoon independent of ingestion of food. Neutrophils die out in showers, as indicated by corresponding increases of nonmotile cells in supravital preparations. They are promptly replaced, either directly from the bone marrow or from a reservoir such as the spleen. It is probable that on stained smears, the nonmotile cells correspond to: (1) cells the cell membranes of which are ruptured, with well stained granules near by; (2) free nuclei with some poorly stained granules in close proximity to the cell; (3) pale cells out of which all the granules seem to have dissolved, leaving a pale structureless cytoplasm. We have occasionally seen large numbers of this third group of cells in severe septic infections, particularly those associated with bacteremia. Motile polymorphonuclear cells in supravital preparations

15. Koskowsky, W., and Zahrzewski, A.: Compt. rend. Soc. de biol. **96**:56, 1927.

16. Beard, L. A., and Beard, J. W.: Am. J. Phys. **85**:169, 1928.

17. Sabin, F. R.: Bull. Johns Hopkins Hosp. **37**:14, 1925; Physical Rev. **8**: 191, 1928.

stained with neutral red show active motion with streaming of granules and staining of granules and vacuoles. The nucleus should not stain if the dye is in correct proportion.

So far as one may apply observations made on laboratory animals and on patients suffering from benign forms of granulopenia to the more severe fatal forms, it seems possible that the mechanism is similar in all. Varying degrees of severity may depend on the duration or the potency of the harmful agent and the constitutional make-up of the individual. Sudden removal of older leukocytes is followed by attempts to replace these by younger forms in a more or less orderly fashion in mild cases. In severe cases there is apparently an abeyance of granulopoiesis, or there may be disorderly distribution with a throwing-out of still more immature forms. In the latter instances, it would appear that the hypothetic chemotactic factor is active while the maturation factor is absent. Clinically, we have seen both of these reactions following arsphenamine therapy; in one, there was produced a granulopenic picture; in the other, a blood picture indistinguishable from myeloblastic leukemia.

In regard to our own experiments, we can only state that a long-continued granulopenia could not be induced in healthy rabbits by the use of a small group of common bacteria in the form of suspension, filtrates or inactivated supernatant fluids. The assumption of a probable altered state of reactivity (from an immunologic point of view) as a factor in these disturbances was not borne out by these results. This, of course, does not dispose of the obscure conditions conveyed by the terms idiosyncrasy or constitutional susceptibility. The positive results in the production of short periods of granulopenia with intravenous injections of peptone and other substances followed by the characteristic influx of young forms on recovery are of interest mainly in their resemblance to milder forms of granulopenia. Although these phenomena are based on well known observations, their application to the granulopenias merits renewed interest and further investigation.

HODGKIN'S DISEASE WITH CAVITY FORMATION IN THE LUNG

REPORT OF A CASE *

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Almost a century ago, Hodgkin described the disease that bears his name. It has many varying clinical and roentgenologic aspects, and has been the subject of numerous publications. The disease invades various organs and systems of the body, and is often difficult to diagnose. Longcope [1] enumerated the possible confusions, and especially stresses our liability to fail in differentiating tuberculosis from Hodgkin's disease. If further investigations substantiate the belief of L'Esperance [2] that the avian tubercle bacillus is responsible for Hodgkin's disease, the similarity and so-called coexistence of the two diseases in one subject will be explained. In discussing a series of 173 cases, in 85 of which there were lesions of the chest, Burnam [3] stated that only 8 presented pleural effusions, but "pictures simulating tuberculosis were commoner." This same difficulty of differentiating the two diseases appears constantly in reports of cases by Longcope,[1] Burnam,[4] Whitaker,[5] Lemon and Doyle,[6] Walton,[7] and others.

Our case is unusual in that roentgenograms taken periodically throughout the period of treating the patient showed the formation

* Submitted for publication, June 17, 1931.

1. Longcope, W. T., in Osler and McCrae: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 5, p. 226.

2. L'Esperance, Elise S.: Studies in Hodgkin's Disease: Cancer; International Contributions to the Study of Cancer in Honor of James Ewing, edited by Frank Adair, Philadelphia, J. B. Lippincott Company, 1931.

3. Burnam, C. F.: Hodgkin's Disease; with Especial Reference to Its Treatment by Irradiation, J. A. M. A. **87**:1445 (Oct. 30) 1926.

4. Burnam, C. F.: Lymphosarcoma and Hodgkin's Disease, W. Virginia M. J. **25**:395 (July) 1929; footnote 3.

5. Whitaker, L. R.: Malignant Lymphoma (Hodgkin's Disease): A Radiographic Study, Arch. Int. Med. **32**:538 (Oct.) 1923.

6. Lemon, W. S., and Doyle, J. B.: Clinical Observations of Hodgkin's Disease with Special Reference to Mediastinal Involvement, Am. J. M. Sc. **162**:516 (Oct.) 1921.

7. Walton, H. J.: Roentgenological Examination of the Mediastinum, Am. J. Roentgenol. **5**:181 (April) 1918.

and continuance of a cavity in the lung. In view of the difficulty, previously mentioned, of differentiating tuberculosis from Hodgkin's disease, this cavity might readily have been thought to be one of a tuberculous nature.

Beside biopsy, which is conclusive in diagnostic value, there is what Whitaker [5] termed the "roentgen-ray therapeutic test"; that is the rapid reduction of the glands under roentgenotherapy. MacRae [8] is even more emphatic than Whitaker; he said, "the hyperplastic glands of Hodgkin's disease respond in an almost spectacular manner to radiation treatment. In fact, shrinking under the influence of x-rays is almost pathognomonic."

Cases in which tuberculosis has been known to be a complicating disease are recorded by Schreiner and Mattick,[9] and Weber.[10] T. B. and T. K. Menon [11] reported a case in which the two, tuberculosis and Hodgkin's disease, existed at the same time. Our case might have been similar to these, and as suggested before, might have been considered tuberculosis, except that when the case came to necropsy, tissue taken from the lining of the cavity proved to be lymphogranulomatous.

A careful review of the literature has failed to reveal another case analogous to ours, though Weber,[10] in February, 1930, reported a case which was diagnosed both clinically and anatomically as bronchial carcinoma, and in which he recorded the roentgenologic finding in the chest of what is "probably a cavity." The existence of this cavity was not substantiated at necropsy. It was only after the microscopic examination of necropsy material that the diagnosis of lymphogranuloma was made, whereas our patient was referred to us for roentgenotherapy for Hodgkin's disease; all the findings were substantiated by necropsy. The first roentgenogram showed that the case belonged to type 1 of the Wessler and Greene [12] classification. It also conformed to the shadow of Hodgkin's disease as described by Childs.[13]

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9. Schreiner, B. F., and Mattick, W. L.: Results of Radiation Therapy in Leukemia and Lymphogranuloma, J. Cancer Research **8**:504 (Dec.) 1924.

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12. Wessler, Harry, and Greene, C. M.: Intrathoracic Hodgkin's Disease: Its Roentgen Diagnosis, J. A. M. A. **74**:445 (Feb. 14) 1920.

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REPORT OF CASE

History.—G. M., a farmer, aged 28, white, was referred to us by Dr. Casper F. Hegner on March 15, 1924, for roentgenograms of the chest and roentgen treatment for Hodgkin's disease. The patient was married, and had one child 4 years old. He was one of six children, all living; his father and mother were living, and all the family were well except his mother who was undergoing treatment at our office for carcinoma of the lip.

The patient had measles, whooping cough, tonsillitis, influenza (1918) and grip often though not severely, and the latest attack occurred four years previously. He smoked a pipe steadily.

Fig. 1.—Roentgenogram of the chest made March, 1924, showing a large mass in the upper mediastinum. Note the increase in soft tissues of the neck.

Eighteen months before consulting a physician, he noticed a lump in the left anterior cervical glands just above the clavicle, and the whole left side of the neck swelled. Fourteen months later, there was a similar involvement of the glands on the right side. The patient said that the glands were larger when he had a cold, and that he caught cold easily, and coughed severely. His normal weight was between 145 and 155 pounds (65.8 and 70.3 Kg.). His appetite was poor, and he had no digestive disturbance other than constipation. He slept poorly on account of difficulty in breathing.

Physical Examination.—The patient was well nourished, weighed 141 pounds (64 Kg.), and was 5 feet 8 inches (172.7 cm.) in height. His pulse was 112, and the blood pressure 130 systolic and 80 diastolic. His tongue was coated, he had a slight shortness of breath, and some hoarseness. His neck was greatly enlarged

on both sides. (Figure 1 shows the increase in soft tissues about the neck.) There were large, diffuse, nonpainful, discrete nodules of different consistency filling the neck on both sides from the clavicles to the upper plane of the thyroid. The larynx was nonadherent. There were enlarged glands in both axillae, and small glands in each groin.

Examination of the chest showed dulness fused with the base of the heart anteriorly, and paravertebral dulness to the seventh dorsal spine posteriorly.

Roentgen examination showed a large, irregular, lobulated mass in the upper mediastinum. All evidences of individual lymph nodes were obliterated (fig. 1).

Course.—Roentgenotherapy resulted in reduction of cervical, axillary and inguinal glands, and relief from symptoms. Roentgenograms taken in February, 1925, eleven months after beginning treatment, showed great reduction of the mass in the upper mediastinum (fig. 2).

Fig. 2.—Roentgenogram taken eleven months later, February, 1925, showing great reduction of the mass in the upper mediastinum.

In January, 1926, the process seemed to be quiescent; in March, the patient had acute coryza with a slight cough which became severe. The following month the mediastinal shadow was even narrower than in January, but there was a large, well defined, homogeneous shadow at the hilus of the right lung, and a small, similar one at the hilus of the left lung (fig. 3). At this time, the roentgenograms began to resemble those described by Wessler and Greene [12] as type 4, "discrete nodes at the roots of the lungs." In October, 1926, there was considerable reduction of the area at the hilus of the right lung, and slight clearing of the one on the left, which had been small before (fig. 4). This reduction followed periodic roentgenotherapy.

Eleven months later, the patient began to lose weight, and reported that he had a cough for the previous month, but no other symptoms. At that time, the roentgenograms showed great increase in the involvement at the hilus of the right lung, infiltration into the right upper lobe, and a moderate sized area in the paren-

Fig. 3.—Roentgenogram taken fourteen months later, April, 1926, showing a narrow mediastinal shadow but a large, well defined, homogeneous shadow at the hilus of the right lung and a small one at the hilus of the left lung.

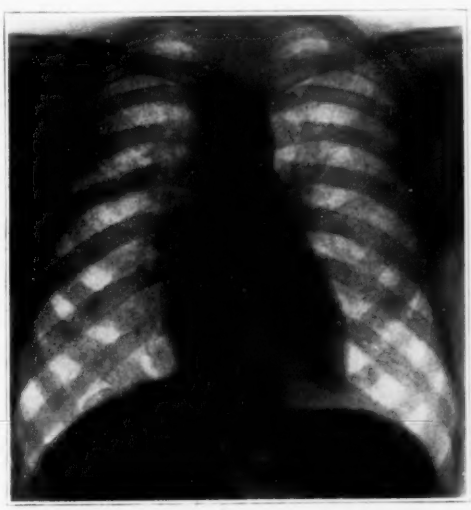

Fig. 4.—Roentgenogram taken six months later, October, 1926, showing the area at the hilus of the right lung to be considerably reduced and the one at the hilus of the left lung to be slightly cleared.

Fig. 5.—Roentgenogram taken eleven months later, September, 1927, showing greatly increased involvement at the hilus of the right lung, infiltration into the right upper lobe, a moderate sized area in the parenchyma of the middle lobe, a small area in the parenchyma of the left upper lobe and increased involvement about the hilus of the left lung.

Fig. 6.—Roentgenogram taken four months later, January, 1928, showing clearing in the area in the middle lobe, a decrease about the hili, but extension of the area in the apex of the right lung.

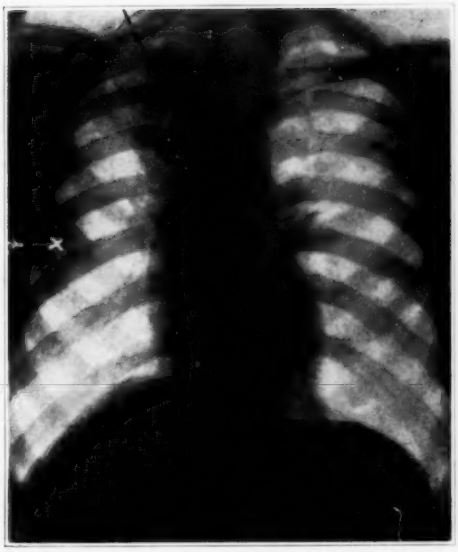

Fig. 7.—Roentgenogram taken one month later, February, 1928, showing an apparently beginning cavity formation in the apex of the right lung and a larger area in the parenchyma opposite the hilus of the right lung.

Fig. 8.—Roentgenogram taken one month later, March, 1928, showing a well defined cavity in the apex of the right lung, an increase in the parenchymatous area opposite the hilus of the right lung and adhesions to the diaphragm on the right.

chyma of the middle lobe. The left lung showed a small area in the parenchyma of the upper lobe, and some increase in the involvement about the hilus (fig. 5).

A second course of treatment was begun at this time, three and one half years after the first series. In January, 1928, four months after instituting treatment, there was clearing of the area in the middle lobe, some decrease in the involvements about the hili, but an extension of the area in the apex of the right lung. Otherwise, the patient's condition was about the same (fig. 6).

Fig. 9.—Photograph of the right lung after necropsy, showing (*A*) cavity in the apex and (*X*) area taken for microscopic section from the wall of the cavity.

One month later, the left lung was unchanged, but the right lung showed what was apparently beginning cavity formation in the apex and a large area of involvement in the parenchyma opposite the hilus (fig. 7).

The patient was uncomfortable and dissatisfied. His cough continued, and in March, 1928, he was referred to one of the large clinics for diagnosis. The report from that group was: "This is a case of chronic fibroid tuberculosis, especially of the right upper lobe, with cavity formation. Only slight adenopathy in the neck and none elsewhere at the present time." Treatment in a sanatorium was advised and it was thought that the case probably had been, but no longer was, Hodgkin's disease. We still maintained that the condition was Hodgkin's disease and not tuberculosis.

However, conforming with the suggestion made at the clinic, the patient was admitted to Agnes Memorial Sanatorium, Denver, on March 23, 1928. At that time, he was short of breath on slight exertion, fatigued easily, had night sweats,

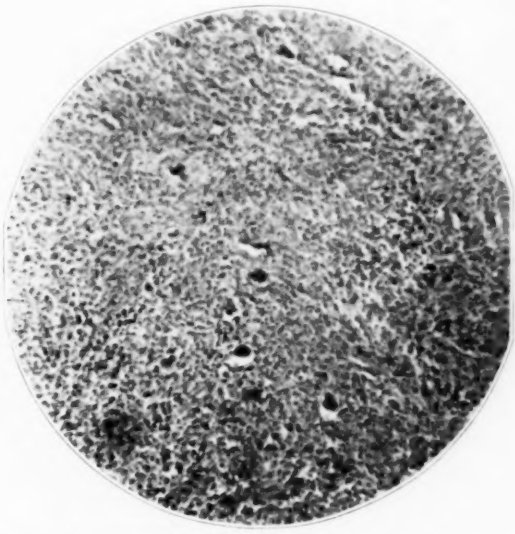

Fig. 10.—Photomicrograph of section taken from the wall of the cavity showing areas of hyaline degeneration surrounded by round or spindle cells in the stroma of the fibrous connective tissue.

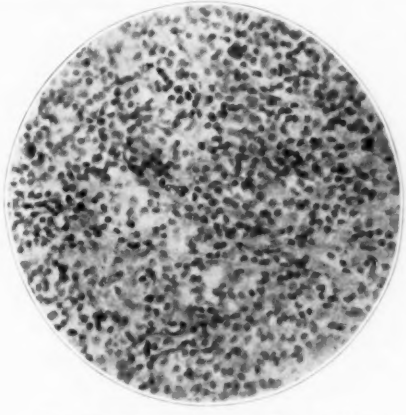

Fig. 11.—Same as figure 10; × 200.

slept poorly (averaged five to six hours) and did not feel rested in the morning. He had pain in the chest at times. He raised one-half cup of purulent sputum daily which was negative for tubercle bacilli on March 12. His weight was 132

pounds (59.9 Kg.), his pulse rate 80 and respiratory rate 20, and his general condition was poor. The breath was foul, the tongue was coated, the mucous membranes and lips were pale, the skin and palms were dry and the fingers were clubbed and cyanotic. There was no cervical, axillary or inguinal adenopathy. The thyroid was nonpalpable.

Examination of the chest showed diminished resonance over the entire right lung, front and back, with increased tactile fremitus; harsh bronchial breathing was heard over the entire upper lobe, and increased dulness over the middle lobe, extending toward the apex; medium to coarse, moist râles were heard down to the fourth rib anteriorly, before and after coughing; none were brought out posteriorly on coughing. There was an amphoric area at the apex indicative of a cavity. On the left, there was diminished resonance over the entire lung with increased tactile fremitus; a few fine to medium râles were heard down to the third rib anteriorly after coughing; none were heard posteriorly.

In the roentgenograms at this time, the cavity in the apex of the right lung was positively defined; there was an increase in the size of the area in the parenchyma opposite the hilus of the right lung, and there were adhesions to the diaphragm on the right. The left lung was practically the same as in February (fig. 8).

No tubercle bacilli were observed in the sputum, though there were questionable acid-fast, clubbed rods in one specimen. Two guinea-pigs inoculated subcutaneously showed no pathologic lesion after three months. Except for a few hyaline casts, the urine was normal.

The medical director of the sanatorium did not concur in the diagnosis of tuberculosis made prior to admission. The patient died of pulmonary hemorrhage on June 3, 1928. Necropsy was performed by Dr. Philip Hillkowitz, the next day.

Postmortem Examination.—The left lung was crepitant throughout, and there was a nodule in the upper lobe measuring 2 cm. in diameter. The right lung was adherent at the apex. There was a nodule in the upper lobe measuring 5 cm. and also a cavity 2 cm. below the apex which measured approximately 6 cm. in diameter. It was free from exudate; the lining was nodular and covered by a smooth membrane. There was a firm, grayish nodule 5 cm. in diameter in the middle lobe. The tracheobronchial lymph nodes were enlarged, firm, and of grayish color (fig. 9). There were no enlarged mesenteric nodes. The spleen showed slight enlargement, but there were no noteworthy changes in the liver or kidneys.

Sections taken through one of the nodules and from the wall of the cavity, when studied microscopically, revealed areas of hyaline degeneration surrounded by round or spindle cells in a stroma of fibrous connective tissue (fig. 10). There were many large, round, deeply stained cells showing several nuclei. These were apparently identical with the Sternberg or Dorothy Reed cells (fig. 11).

The anatomic diagnosis was lymphogranulomatosis of the lung with cavity formation.

COMMENT

The case presented is one of lymphogranuloma of the mediastinal type, which in its later stages closely resembled tuberculosis. It was exceptional in that it developed a true cavity in the lung which also proved to be lymphogranulomatous when the case came to necropsy. We have been unable to find a similar case reported in the literature.

246 Metropolitan Building.

HEMANGIECTATIC HYPERTROPHY AND CONGENITAL PHLEBARTERIECTASIS

WITH PARTICULAR REFERENCE TO THE DIAGNOSTIC IMPORTANCE OF THE PERIPHERAL VASCULAR PHENOMENA *

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The purpose of this communication is to present observations that should be helpful in the diagnosis of hemangiectatic hypertrophy. The term "hemangiectatic hypertrophy of a limb" denotes a condition of hypertrophy associated with increased vascularity of the affected extremity. This congenital or developmental increased vascularity may be due to dilatation of both the arteries and the veins, the term "congenital or developmental phlebarteriectasis" then being applied. Certain cirsoid aneurysms and plexiform hemangiomas of the scalp and face are probably of this nature. When the dilatation of the vessels is confined almost entirely to the veins, the term phlebectasis is applied. It should be noted that in phlebarteriectasis abnormal direct artery to vein anastomoses are not necessarily present, and that this condition is therefore to be differentiated from the more common traumatic or congenital arteriovenous aneurysms.

Fourteen cases of hemangiectatic hypertrophy recorded up to 1918 were summarized by F. Parkes Weber.[1] The reports of cases available for study will not be reviewed here, but references to these reports are given.[2]

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* From the Medical Research Laboratories of the Beth Israel Hospital and the Department of Medicine, Harvard Medical School.

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2. Weber (footnote 1). Harris, K. E., and Wright, G. P.: A Case of Haemangiectatic Hypertrophy of a Limb and Observations upon Rate of Growth in the Presence of Increased Blood Supply, Heart **15**:141, 1930. Lewis, D.: Congenital Arteriovenous Fistula, Lancet **2**:621, 680, 1930. Pemberton, J. J., and Saint, J. H.: Congenital Arteriovenous Communications, Surg., Gynec. & Obst. **46**:470, 1928.

REPORT OF CASE

History.—N. B., a schoolgirl, 15 years of age, was admitted to the hospital for study on Feb. 16, 1931. When she was 2 years old, the left hand was observed to be noticeably warmer than the right, and the veins of the left hand were unduly prominent. There was no history of trauma. As the patient grew older, the left hand and arm became larger and longer than the right. Six years before admission an operation was performed at another hospital in an attempt to correct the condition. The antecubital fossa was incised, but no abnormal artery to vein communications were found. The patient has felt entirely well. She states that the left hand and the lower part of the left arm feel warmer than the right and tend to perspire more readily.

Examination.—Physical examination showed a bright, intelligent girl with no abnormalities save those related to the left arm and the vascular system. The heart was normal in size and position. The heart sounds were of good quality, and a soft systolic murmur was heard everywhere over the precordial area, particularly at the apex. Retrosternal dulness was normal in extent. In the left supraclavicular region coarse systolic and diastolic thrills were palpable, and systolic and diastolic murmurs could be heard. These signs were not transmitted into the left carotid artery but were easily elicited over the vessels of the left arm and forearm. A systolic thrill could be felt on grasping the left upper extremity firmly at any level between the apex of the axilla and the tips of the fingers. No evidence of abnormalities of intracranial blood vessels was present. Ophthalmoscopic examination of the fundi showed normal findings.

Capillary pulsation was visible in the fingers of both hands and over the forehead after it was stroked. These pulsations did not disappear after the left subclavian artery was compressed to the point of occlusion.

The patient was right-handed, but the left arm was obviously larger and longer than the right. At the medial border of the left antecubital fossa, there was an old, irregular scar measuring 7 cm. by 2 cm. in the greatest diameters. Beginning a short distance above the left elbow and increasing gradually in intensity down the arm, dusky cyanosis was evident (fig. 1). The finger-nails and finger-tips of all the fingers of the left hand showed a more reddish cyanosis. The fingers of the left hand were longer and more slender than those of the right hand. Several small, red, irregular, cutaneous angiomas, varying from 0.5 to 2.5 cm. in diameter were present over the left forearm and lower third of the left arm, particularly on the extensor surface. The color of these angiomas varied considerably in intensity on different occasions. The left brachial, radial and ulnar arteries were dilated and forcibly pulsating. Pulsation of the anterior interosseous artery was easily felt in the lower part of the left forearm. The veins of the left forearm and particularly those of the hand were abnormally dilated and prominent. The engorgement of what virtually amounted to a venous plexus over the fingers, hand and lower part of the forearm became conspicuous when the hand was placed in a dependent position. With the left arm 6.5 cm. below the level of the right auricle, definite systolic pulsations were visible in the veins over the back of the left hand.

Heat, cold, touch, pain and pressure perception were normal. There was no astereognosis.

The red and white blood cell counts were within the limits of normal. Repeated urinalyses revealed no abnormalities. The Wassermann, Kahn and Hinton reactions of the blood of the patient and of the patient's mother were negative.

Special Studies.—Electrocardiographic tracings were normal. Roentgenograms of the chest showed no abnormalities. The cardiac measurements from teleroentgenograms were as follows: from midsternum to right border of heart, 3.4 cm.;

Fig. 1.—Hemangiectatic hypertrophy and congenital phlebarteriectasis of the left arm, showing the hypertrophy, cyanosis and cutaneous angiomas of the left forearm and hand and the prominent veins over the hand and lower part of the forearm.

Fig. 2.—Roentgenogram of the forearms, showing the increased length of the left radius and ulna.

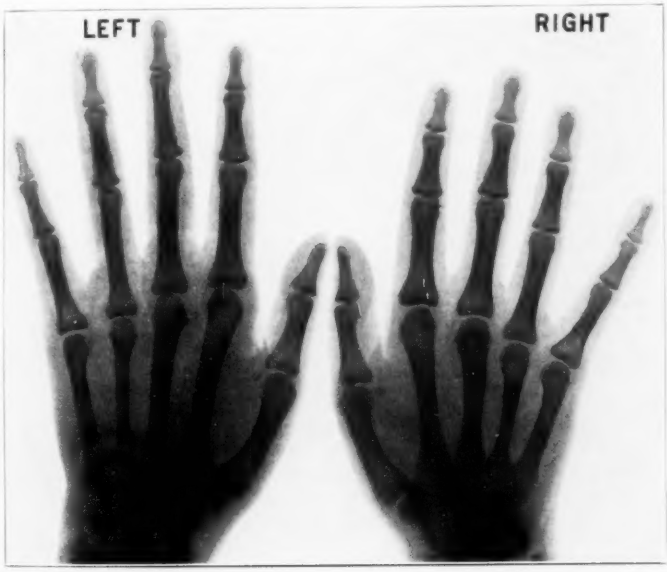

Fig. 3.—Roentgenogram of the hands, showing the increased length of the metacarpal bones and phalanges of the left hand.

TABLE 1.—*Linear Measurements of Bones of Upper Extremities*

Bone	Right, Cm.	Left, Cm.	Difference, per Cent
Humerus	33.2	34.0	2
Ulna	25.4	28.4	12
Radius	23.9	26.8	12
Metacarpals			
Thumb	4.6	5.0	9
Index	6.6	7.1	8
Middle	6.1	6.6	8
Ring	5.4	5.9	9
Little	5.3	5.7	8
Proximal phalanges			
Thumb	3.0	3.0	0
Index	4.6	5.0	8
Middle	4.3	5.0	16
Ring	4.1	4.8	17
Little	3.2	3.7	16
Middle phalanges			
Index	2.5	2.7	8
Middle	2.9	3.4	16
Ring	2.7	3.1	15
Little	1.9	2.2	16
Terminal phalanges			
Thumb	2.3	2.2	−4
Index	1.8	1.8	0
Middle	1.8	1.9	6
Ring	2.0	2.1	5
Little	1.7	1.7	0

TABLE 2.—*Surface Measurements of Upper Extremities*

	Right, Cm.	Left, Cm.	Difference, per Cent
Lengths			
Tip of acromion process to styloid process of radius	52.2	57.0	9
Tip of acromion process to external condyle of humerus	29.8	30.5	2
Olecranon process of ulna to styloid process of ulna	25.4	28.3	11
Styloid process of radius to tip of middle finger	18.8	19.5	4
Base of proximal phalanx to tip of finger			
Thumb	6.1	6.2	2
Index	9.7	10.5	8
Middle	10.5	11.6	11
Ring	10.1	11.1	10
Little	8.0	8.5	6
Circumferences			
Arm at upper border of axilla	27.5	28.4	3
Arm, middle	22.9	24.6	7
Arm above condyles of humerus	21.0	23.2	10
Forearm, below elbow	22.0	23.8	8
Forearm, midportion	19.4	20.0	3
Forearm, above head of ulna	15.2	15.2	0
Hand at metacarpal phalangeal joint	18.4	18.8	2
Fingers			
Thumb, terminal phalanx, midportion	5.5	5.2	−5
Index, middle phalanx, midportion	5.1	4.9	−4
Middle, middle phalanx, midportion	5.1	4.6	−10
Ring, middle phalanx, midportion	4.8	4.4	−8
Little, middle phalanx, midportion	3.9	3.8	−3

TABLE 3.—*Surface Areas of Upper Extremities*

	Right, Sq.Cm.	Left, Sq.Cm.	Difference, per Cent
Arm and forearm	1,032	1,174	14
Hand	384	407	6
Total upper extremity	1,416	1,581	12

from midsternum to left border of heart, 7.4 cm.; total transverse diameter, 10.8 cm.; transverse diameter of great vessels, 4.5 cm.; transverse diameter of chest, 23.9 cm. Similar measurements from a teleroentgenogram taken during digital occlusion of the left subclavian artery showed no change.

Fluoroscopic observation of the heart shadow showed no perceptible changes in the cardiac excursion before and during digital occlusion of the left subclavian artery.

TABLE 4.—*Measurements of Cubic Volumes of Both Upper Extremities*

Part of Extremity Measured	Right, Cc.	Left, Cc.	Increase	
			Cc.	Per Cent
Arm	1,565	1,620	55	3
Forearm	750	935	185	24
Hand	285	345	60	21

TABLE 5.—*Measurements of Skin Temperature* *

Site of Measurement	Right, Degrees Centigrade	Left, Degrees Centigrade	Difference, Degrees Centigrade
Angle of jaw	31.2	31.1	0.9
Infraclavicular fossa	31.4	31.4	0.0
Arm			
Over head of humerus	31.4	31.8	0.4
Midportion, extensor surface	31.1	31.7	0.6
Midportion, flexor surface	31.7	32.5	0.8
Forearm			
Midportion, extensor surface	31.3	31.7	0.4
Midportion, flexor surface	32.1	33.0	0.9
Wrist			
Extensor surface	31.3	33.1	1.8
Flexor surface	32.3	33.2	0.9
Hand			
Dorsal surface	32.0	33.7	1.7
Palmar surface	32.3	33.4	1.1
Thumb			
Proximal phalanx, dorsal surface	32.2	32.3	0.1
Proximal phalanx, palmar surface	32.3	32.1	−0.2
Second phalanx of fingers, dorsal surface			
Index	32.3	33.1	0.8
Middle	32.4	33.5	1.1
Ring	32.2	33.6	1.4
Little	32.3	33.3	1.0
Second phalanx of fingers, palmar surface			
Index	31.4	33.4	2.0
Middle	31.8	33.9	2.1
Ring	31.6	33.5	1.9
Little	31.2	33.7	2.5
Tips of fingers			
Thumb	32.6	32.0	−0.6
Index	32.7	32.4	−0.3
Middle	32.7	33.0	0.3
Ring	32.6	33.3	0.7
Little	32.6	32.7	0.1

* The measurements given are those actually recorded at room temperature of 23 C. and are not corrected to the standard temperature of 20 C.

Roentgenographic films of both upper extremities showed that the bones of the right arm were normal, while those of the left arm and hand were definitely longer (figs. 2 and 3). Measurements of the bones of both upper extremities are recorded in table 1. Surface measurements of both arms are given in table 2. The surface area of the right upper extremity, calculated according to the formula of Du Bois,[3] was 1,416 sq. cm.; of the left upper extremity, 1,581 sq. cm. The surface areas of the arms and hands are presented in table 3. The cubic volume of each arm, measured by water displacement, is given in table 4.

3. Du Bois, E. F.: Basal Metabolism in Health and Disease, Philadelphia, Lea & Febiger, 1924.

The temperature of the skin of the left upper extremity, particularly of the lower part of the forearm and hand, was perceptibly higher than that over corresponding areas of the right arm. A résumé of the measurements that were made with a thermocouple is given in table 5.

Numerous measurements of the arterial blood pressure were made independently by two observers. The blood pressure in the right brachial artery, taken by means of a standard mercury manometer, averaged 114 mm. of mercury systolic and 64 mm. of mercury diastolic; that in the left brachial artery, 128 mm. of mercury systolic and 54 mm. of mercury diastolic. Digital occlusion of the left subclavian artery caused a rise, on the average, of 10 mm. of mercury in the right brachial diastolic blood pressure; the systolic blood pressure remained unchanged. Compression of the right subclavian artery caused no change in the left brachial blood pressure. The femoral arterial blood pressures of the right and left legs were equal; the average of numerous readings was 112 mm. of mercury systolic and 66 mm. of mercury diastolic. The differential pressure sign of Hill and Rowlands [4] was not elicited. Digital compression of the left subclavian artery

TABLE 6.—*Measurements of Capillary and Arteriolar Blood Pressures*

	Capillary Pressure		Arteriolar Pressure	
Site of Measurement	Right, Mm. Hg	Left, Mm. Hg	Right, Mm. Hg	Left, Mm. Hg
Arm, upper portion	10	10	45	45
Forearm, lower portion	9	11	55	60
Sternum	11		48	

caused a rise in the femoral diastolic blood pressure of 12 to 18 mm. of mercury. The blood pressure readings of the leg were made by means of a special cuff, 20 cm. in width.

Measurements of the capillary and arteriolar blood pressure [5] were made according to the method used by Lewis and Haynal [6] and by Ellis and Weiss,[7] all measurements being made with the closed capsule. A summary of the measurements is presented in table 6. Each figure represents the average of many observations made independently by two observers. There is no significant difference between the measurements made on the two arms. The results are normal and do not indicate diminution in the peripheral resistance of the cutaneous vessels.

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4. Hill, L., and Rowlands, R. A.: Systolic Blood Pressure: (1) In Change of Posture; (2) In Cases of Aortic Regurgitation, Heart **3**:219, 1912.

5. By capillary pressure is meant the pressure necessary to cause minimal distinct blanching of the skin by compression of subpapillary venules (Blumgart, H. L.; Lawrence, J. S., and Ernstene, A. C.: The Dynamics of the Circulation in Coarctation [Stenosis of the Isthmus] of the Aorta of the Adult Type, Arch. Int. Med. **47**:811 [May] 1931).

6. Lewis, T., and Haynal, I.: Observations Relating to the Tone of the Minute Vessels of the Human Skin, with Remarks upon and Illustrations of Measurements of Pressure Within These Vessels, Heart **14**:177, 1928.

7. Ellis, L. B., and Weiss, S.: The Measurement of Capillary Pressure Under Natural Conditions and After Arteriolar Dilatation in Normal Subjects and in Patients with Arterial Hypertension and with Arteriosclerosis, J. Clin. Investigation **8**:47, 1929.

The venous pressures in the right and left antecubital veins were measured according to the direct venipuncture method of Moritz and Tabora.[8] The corrected results of several measurements of the venous pressure in the right arm averaged 10.2 cm. of water; in the left arm, 23.8 cm. of water.

The bradycardiac reaction was tested. The ventricular rate under resting conditions averaged 84 beats per minute. Digital compression of the left subclavian artery was followed by immediate lowering of the ventricular rate to approximately 68 beats per minute. The time interval between compression of the vessel and the onset of slowing in rate was measured by sudden application of pressure to the upper part of the left arm by means of a large pressure bottle while a continuous electrocardiographic tracing was taken. These observations were repeated on several occasions. The decrease in ventricular rate occurred

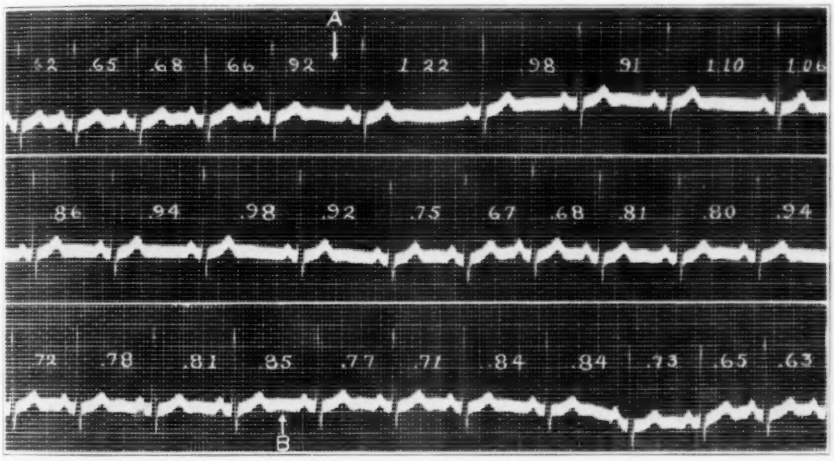

Fig. 4.—Electrocardiographic tracing illustrating the bradycardiac reaction produced by sudden application of pressure to the upper part of the left arm. The pressure was applied at (*A*) and discontinued at (*B*). Slowing of the ventricular rate is evident in the first cardiac cycle following the application of pressure. A secondary slight quickening in rate occurs after the first 10 beats. The R-R intervals are indicated in seconds.

as early as 0.09 seconds after the application of pressure. In practically all instances, the slowing was evident in the first cycle following the application of pressure (fig. 4). The lowering in ventricular rate was most pronounced immediately after pressure into the armlet, a secondary slight quickening in rate frequently occurring after the first ten or twelve beats. No change in the contour of the complexes was observed.

8. Moritz, F., and Tabora, D.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, Deutsches Arch. f. klin. Med. **98**:475, 1910.

The volume of the blood and of the plasma were measured by the brilliant vital red dye method used by Thompson.[9] The results are presented in table 7, and are within the limits of normal.

Duplicate measurements were made of the oxygen content and capacity of blood from the right radial artery, right antecubital vein, left radial artery and left antecubital vein. The Van Slyke-Neill manometric apparatus was used. The results are presented in table 8.

Measurements of the velocity of blood flow were made by means of the radioactive method.[10] After the radioactive substance was injected into the antecubital vein, the time necessary for the substance to traverse the veins to the right auricle, as well as the time necessary for the substance to pass through the pulmonary

TABLE 7.—*Measurements of Blood and Plasma Volume*

	Average Normal Values, Cc.	Observed Values, Cc.
Total plasma volume	3,550	2,482
Total blood volume	6,035	4,140
Plasma volume per kilogram	50	43
Blood volume per kilogram	85	72

TABLE 8.—*Blood Gas Measurements*

	Oxygen Content		Oxygen Capacity		Percentage Saturation		Arteriovenous Oxygen Difference	
Source of Blood	Right, per Cent by Volume	Left, per Cent by Volume	Right, per Cent by Volume	Left, per Cent by Volume	Right, per Cent by Volume	Left, per Cent by Volume	Right, per Cent by Volume	Left, per Cent by Volume
Radial artery	17.3	17.1	18.0	18.1	96	95		
Antecubital vein	14.3	17.1	17.7	18.2	81	94	3.0	0

TABLE 9.—*Measurements of Velocity of Blood Flow*

Site of Injection	Arm to Heart Time, Seconds	Pulmonary Circulation Time, Seconds
Right antecubital vein	7.5	9.0
Left antecubital vein	1.5	8.5

circulation, was measured.[11] A summary of the measurements is presented in table 9. The pulse rate at the time of the measurements was 75; it was not

9. Thompson, W. O.: Studies in Blood Volume: I. The Blood Volume in Myxedema with a Comparison of Plasma Volume Changes in Myxedema and Cardiac Edema, J. Clin. Investigation **2**:477, 1926.

10. Blumgart, H. L., and Yens, O. C.: Studies on the Velocity of Blood Flow: I. The Method Utilized, J. Clin. Investigation **4**:1, 1927. Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow: II. The Velocity of Blood Flow in Normal Resting Individuals, and a Critique of the Method Used, ibid. **4**:15, 1927.

11. Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow: VII. The Pulmonary Circulation Time in Normal Resting Individuals, J. Clin. Investigation **4**:399, 1927.

significantly altered by the procedure. The venous pressure in the right arm at the time of the injection into the vein of that arm was equivalent to 11.5 cm. of water; the venous pressure in the left arm at the time of the injection into the vein of that limb was 23.6 cm.

The volume flow of blood per minute through the lungs (cardiac volume output per minute) was measured by the acetylene method of Grollman [12] both before and during occlusion of the vessels of the left arm. A summary of the measurements is presented in table 10. The flow before occlusion was 2.7 liters per minute; during occlusion, 2.9 liters per minute. The absence of any change may well have been due to the inapplicability of this type of method in the presence of free arteriovenous communication; the abnormally rapid return of blood [13] from the left arm, as shown by the velocity of studies of blood flow, probably introduces an appreciable error. The measurements made while the left brachial artery was occluded may be regarded with greater confidence. They are practically within the limits of normal as observed by Grollman.[14]

The tourniquet test was made as follows: With the patient in the supine position and the arm held upright to facilitate venous return, the blood supply to each arm was suddenly interrupted by means of a pneumatic cuff. When the arm was

TABLE 10.—*Measurements of Cardiac Volume Output per Minute*

	Oxygen Consumption, Cc. per Minute	Arteriovenous Oxygen Difference, Cc. per Liter of Blood	Cardiac Minute Volume Output	
			Total, Liters	Per Square Meter of Body Surface, Liters
Without occlusion of arteries of left arm.....	187	70	2.7	1.7
With occlusion of arteries of left arm.....	187	66	2.9	1.8

lowered to the horizontal position and the pressure then released, a flush appeared in the skin of the extremity after a short interval. Repeated observations showed that the time of appearance of the flush was identical in the two arms, the average being 2.8 seconds after release of the pressure in the left arm and 2.9 seconds in the right arm. These results are in accord with the measurements of arteriolar and capillary blood pressure, and indicate that the peripheral resistance in the cutaneous vessels of the two arms is equal and normal.

COMMENT

Detailed study of uncommon disease states is important particularly for two reasons: 1. The rarity of a condition and consequent lack of adequate information may lead to faulty diagnosis and treatment.

12. Grollman, A.: Determination of Cardiac Output of Man by Use of Acetylene, Am. J. Physiol. **88**:432, 1929.

13. Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow: X. The Relation Between the Velocity of Blood Flow, the Venous Pressure and the Vital Capacity of the Lungs in Fifty Patients with Cardiovascular Disease Compared with Similar Measurements in Fifty Normal Persons, J. Clin. Investigation **5**:379, 1928.

14. Grollman, A.: Physiological Variations in the Cardiac Output of Man: VI. The Value of the Cardiac Output of the Normal Individual in the Basal Resting Condition, Am. J. Physiol. **90**:210, 1929.

2. Pathologic abnormalities frequently provide an opportunity to study in isolated form certain mechanisms that increase our understanding of common conditions. The study of hemangiectatic hypertrophy reported here exemplifies both of these points. Lack of appreciation of the meaning of some of the clinical signs had led to fruitless surgical intervention at a point remote from the actual site of the lesion; the present detailed study of the peripheral blood flow has led to a fuller understanding of certain vascular phenomena that occur more commonly in other disease states.

The general manifestations of abnormally free arteriovenous communication observed in our patient may be considered conveniently under the following six headings:

1. *Arterial Blood Pressure.*—Taking the pressure in the right brachial artery as an index of the general arterial pressure, the systolic pressure of 114 mm. of mercury may be considered normal; the diastolic pressure of 64 mm. of mercury was somewhat below normal. Lowering of the diastolic pressure is frequently more pronounced in cases of direct arteriovenous anastomosis with large fistulas, and is due to leakage of blood through the abnormal opening during diastole. The effect in our patient of the abnormal leakage of blood from arteries to veins on the general diastolic arterial pressure is shown by the fact that closing the left subclavian artery repeatedly caused a rise in the right brachial diastolic pressure, the average increase being 10 mm. of mercury. The increase observed in femoral diastolic blood pressure when the left subclavian artery was occluded is of similar significance. Compression of the right subclavian artery, on the other hand, did not affect the left brachial diastolic blood pressure.

In the left brachial artery the systolic blood pressure averaged 14 mm. of mercury higher, and the diastolic blood pressure, 6 mm. of mercury lower than in the right brachial artery. Both the elevated systolic pressure and the lowered diastolic pressure in the left arm were a direct expression of the local anatomic conditions. The lowering of the diastolic blood pressure in the left arm below that of the rest of the body was due to the proximity of the leakage of blood from artery to vein. At first glance, the relatively high left brachial systolic blood pressure appears strange; if the arteriovenous communications were proximal to the brachial artery, the abnormal leakage should cause a lowering in pressure, while if the abnormal communications were distal to the brachial artery, the blood pressure might not be affected. The locally elevated systolic blood pressure in the left arm may be explained, however, by the following considerations: The arterial pressure is highest in the larger trunks, such as the aorta, and undergoes diminution in the smaller vessels according to the resistance offered by their

decrease in caliber. William Hunter,[15] in 1762, and other observers [16] since that time noted that arteries proximal to arteriovenous communications are dilated and therefore offer less frictional resistance. The systolic pressure in a dilated peripheral artery consequently approximates more nearly the pressure existing in the larger central trunks. In our patient the left brachial artery was obviously dilated and the left subclavian artery probably had undergone a similar change, since its pulsation prominently encroached on the left supraclavicular fossa. The locally elevated systolic blood pressure in the left brachial artery is thus accounted for.

2. *Bradycardiac Reaction.*—Obliteration of abnormal arteriovenous communications or occlusion of the principal arteries leading to such communications causes a slowing of the heart rate; the degree of slowing is related to the amount of blood passing through such openings. This phenomenon, as pointed out by Dean Lewis,[17] was first described by Nicoladoni [18] in 1875 and by Israel [19] in 1877. In our patient, digital compression of the left subclavian artery or application of pressure about the upper part of the left arm produced an abrupt fall in the heart rate, the average decrease being 16 beats per minute. A slight secondary increase in ventricular rate was noted during maintenance of the compression. The extraordinarily brief interval between arterial occlusion and the bradycardiac reaction is in accord with evidence that the reaction is mediated through a reflex nerve mechanism. Lewis and Drury,[20] and Nanu, Alexandrescu-Dersca and Lazeanu [21] were able to abolish the bradycardiac reaction by atropinization.

3. *Elevation in Venous Pressure.*—In our subject, the venous pressure in the affected arm was greatly elevated, while the general venous pressure of the body, as gaged by the pressure in the right

15. Hunter, W.: Further Observations upon a Particular Species of Aneurysm, Med. Obs. Soc. Phys. **2**:390, 1762.

16. Reid, M. R.: The Effect of Arteriovenous Fistula upon the Heart and Blood-Vessels: An Experimental and Clinical Study, Bull. Johns Hopkins Hosp. **31**:43, 1920. Callander, C. L.: Study of Arterio-Venous Fistula with an Analysis of 447 Cases, Johns Hopkins Hosp. Rep. **19**:259, 1920.

17. Lewis (footnote 2, third reference).

18. Nicoladoni: Phlebarteriektasie der oberen Extremität, Arch. f. klin. Chir. **18**:252, 1875.

19. Israel, J.: Angiektasie im Strombegiete der Arteria tibialis anterior, Arch. f. klin. Chir. **21**:109, 1877.

20. Lewis, T., and Drury, A. N.: Observations Relating to Arterio-Venous Aneurism: I. Circulatory Manifestations in Clinical Cases with Particular Reference to the Arterial Phenomena of Aortic Regurgitation, Heart **10**:301, 1923.

21. Nanu, I.; Alexandrescu-Dersca, C., and Lazeanu, E.: Les troubles cardiaques consécutifs aux anévrismes artério-veineux, Arch. d. mal. du coeur **15**:829 1922.

antecubital vein, was within the upper limits of normal. Local elevation of the venous pressure in the vicinity of abnormal arteriovenous anastomosis was observed by Lewis and Drury;[22] they also noted that the general venous pressure of the body was within the limits of normal. In the absence of evidence of venous obstruction in the left arm of our patient and in the absence of myocardial insufficiency, one must assume that the increased pressure in the veins of the left arm was due to a leakage of arterial pressure through the abnormal artery to vein communication. The elevated venous pressure in the left arm did not affect the general venous pressure in the rest of the body; repeated observations before and again during compression of the left subclavian artery showed no variation in the venous pressure readings of the right arm.

4. *Thrills and Murmurs in Peripheral Vessels.*—Systolic and diastolic murmurs and thrills were evident over the subclavian and brachial vessels. These signs are evidence of abnormal arteriovenous communications.[23] The pathologic physiology of these signs and their significance in the diagnosis of the exact site and nature of the abnormal arteriovenous communication will be discussed.

5. *Systolic Venous Pulsation.*—With the hand of the left arm 6.5 cm. below the level of the right auricle, systolic pulsation of the veins of the back of the hand were plainly visible. This finding was interpreted as additional evidence of free arteriovenous communication.

6. *Blood Gas Measurements.*—The oxygen content of blood from the antecubital vein of the right arm was 3 per cent by volume less than that of blood from the right radial artery. This difference in oxygen content is within the limits of normal. There was no significant difference in the oxygen content of the blood from the left radial artery and that from the left antecubital vein (table 8). The arterial nature of the venous blood of the left arm indicates a conspicuously increased rate of flow through capillary vessels or a flow of blood from artery to vein which is relatively direct so that little opportunity is afforded for the giving-off of oxygen. At least a significant part of the abnormal flow from artery to vein was probably transported through dilated capillaries, for otherwise it is difficult to understand such phenomena as the increased growth of the affected parts.

We are unable to state the exact degree of increase in blood flow through the left upper extremity. The relatively moderate rise in general diastolic blood pressure of the body following occlusion of the abnormally dilated vessels, the absence of any change in the cardiac outlines after obliteration of the arterial leakage and the absence of

22. Lewis and Drury (footnote 20, cases 1 and 2).
23. Callander (footnote 16, reference 2).

cardiac hypertrophy indicate, however, that the amount of blood shunted through the dilated channels, while considerable, did not add greatly to the total blood flow of the body.

Diagnosis of Site and Nature of the Arteriovenous Communication.—The phenomena described in the foregoing paragraphs are the result of abnormally free communication between the arterial and venous systems. They do not denote whether the artery and vein communicate by direct anastomosis or by intermediate vascular plexuses. The mechanism of production of the murmurs and thrills in the peripheral vessels and the direction of transmission of these signs differ so widely from similar phenomena observed more commonly in cardiovascular disease that detailed study is necessary for accurate localization of the site of the lesion. In point of fact, the presence of thrills and murmurs in the brachial and subclavian vessels of our patient had led to a mistaken diagnosis of arteriovenous aneurysm and fruitless surgical intervention. We were inclined to make the same diagnosis after our first superficial examination but hesitated because of certain phenomena that were not in accord with this view of the condition. These phenomena were as follows:

1. Direction of venous blood flow. By stripping small segments of veins on the back of the left hand of their blood content and then releasing the distal portion, the veins were observed to fill immediately. When this procedure was repeated, but with release of the proximal portions first, filling took place very slowly. This observation indicated that the flow of venous blood was natural in its direction. If a direct artery to vein anastomosis had been present in the subclavian or brachial vessels, the flow of blood might have been reversed in some of the veins, or at least retrograde filling might have occurred. Such retrograde filling did in fact occur, but only when the arm was suspended at the side with the back of the hand 42 cm. below the level of the right auricle. This finding was interpreted as due to incompetency of the valves of the veins, the situation under such circumstances being similar to that in varicose veins of the legs.

2. Effect of arterial occlusion on venous pulsation and engorgement. Compression of the left subclavian or of the left brachial artery caused disappearance of the pulsation and diminution in the engorgement of the veins of the back of the left hand. Compression of the radial and ulnar arteries singly was without this effect, but simultaneous compression of both vessels was immediately followed by the disappearance of the pulsation of the veins and by the lessening of their engorgement. These observations suggested that the arteriovenous communication was at or distal to the site of the radial and ulnar artery

compression. If the communication had been proximal to this level, compression should have increased the arterial leakage and led to more prominent venous pulsation and increased venous filling.

This tentative localization of the arteriovenous communications was next tested more critically. A needle communicating with a manometer filled with a solution of sodium citrate was inserted into the left antecubital vein. The venous pressure at this time was equivalent to 21 cm. of water. With the needle freely communicating with the lumen of the antecubital vein, pressure above arterial systolic was applied over the lower ends of the left radius and ulna. The venous pressure immediately decreased to 15.2 cm. When the pressure at the wrist was released, the venous pressure immediately rose to 20.3 cm. These measurements demonstrated that the main communications between artery and vein were in large part at or distal to the lower ends of the radius and ulna.

3. Effect of arterial occlusion on general diastolic blood pressure. A rise in general diastolic blood pressure on compression of the arteries in the left arm may likewise be regarded as an indication that the abnormal leakage of blood occurs at or distal to the point of compression. This phenomenon may consequently be utilized as a test for localizing the site of the lesion. Artery compression distal to the site of the abnormal artery to vein communication would be either without effect, or, by favoring the leakage of blood into the veins would cause, instead of a rise, a further lowering in general diastolic blood pressure. The effect on the general arterial blood pressure as gaged by measurements of the right brachial systolic and diastolic pressures was observed, accordingly, after compression of the vessels at the mid-portion of the left arm and forearm. A definite rise in the diastolic pressure was uniformly elicited. A similar increase was produced by compression at the lower ends of the radius and ulna by means of a pneumatic cuff. The rise in diastolic blood pressure after compression at the mid-arm, mid-forearm and lower ends of the radius and ulna was as great as that produced by digital occlusion of the left subclavian artery. Since the magnitude of the rise in diastolic pressure is closely related to the amount of decrease in arterial blood leakage, these observations suggest that the principal abnormal artery to vein communications in our subject were at or below the level of the wrist.

4. Bradycardiac reaction. The lowering of the ventricular rate caused by compression of the left subclavian artery was due to cessation of the abnormal leakage of arterial blood into the veins. The slowing in the ventricular rate on the compression of an artery signifies that the abnormal arteriovenous communication lies in the segment of artery compressed or in its peripheral continuations. Accordingly, suc-

cessive measurements of the ventricular rate were made after obliteration of the vessels at the middle upper part of the arm and at the middle portion of the forearm by means of a pneumatic cuff. Repeated observations uniformly showed a fall of from 13 to 20 beats per minute in the ventricular rate. Simultaneous digital compression of the radial and ulnar arteries just above the wrist showed a similar lowering of the heart rate, again indicating that the principal abnormal anastomoses were either at or distal to the wrist.

5. Site of greatest increase in blood flow. Measurements of the actual volume of blood flow in various portions of the arm are not practicable. One would expect, however, that the greatest degree of hypertrophy and the greatest increase in skin temperature would occur in those regions where blood flow was most conspicuously increased. Linear measurements of the bones (table 1) and volume measurements of the hands, forearms and arms (table 4) showed the greatest changes evident in the left hand and left forearm. These measurements do not disclose whether the predominant changes in the forearm occur in its upper or lower portions. It is significant, however, that the measurements of skin temperature (table 5), which allow of more accurate localization, showed the greatest increase over the left hand and the lower part of the left forearm, and that the only bones that showed abnormal erosions were the middle phalanx of the left middle finger and the proximal phalanges of the left middle and ring fingers. These grooves were probably due to pressure atrophy caused by vigorous pulsation of abnormally dilated vessels;[24] this phenomenon is similar to the erosion of ribs observed in patients with coarctation of the aorta.[25] Although the aforementioned considerations indicate that the principal abnormal artery to vein leakage occurred at the wrist and in the hand, the lesion was probably not sharply demarcated but may have involved, to some extent, the middle and upper parts of the forearm. Evidence of the latter was suggested by the presence of cutaneous angiomas over these regions.

6. Observations on the arterial murmurs and thrills. The systolic murmur and thrill over the left subclavian artery and over the left brachial artery were readily understandable on the basis of abnormal communications in the metacarpus and carpus. Duroziez' sign and

24. Ernstene, A. C., and Robins, S. A.: The Roentgenoglogic Diagnosis of Stenosis of the Descending Arch (Coarctation) of the Aorta, Am. J. Roentgenol. **25**:243, 1931.

25. Railsback, O. C., and Dock, W.: Erosion of the Ribs Due to Stenosis of the Isthmus (Coarctation) of the Aorta, Radiology **12**:58, 1929. Blumgart, H. L.; Lawrence, J. S., and Ernstene, A. C.: The Dynamics of the Circulation in Coarctation (Stenosis of the Isthmus) of the Aorta of the Adult Type: Relation to Essential Hypertension, Arch. Int. Med. **47**:806 (May) 1931.

the diastolic thrill over these vessels were not so readily explicable. Occurring frequently in aortic regurgitation, Duroziez' sign is commonly attributed to a retrograde flow of blood during diastole. A diastolic reflux of blood in our patient could be hypothecated only if the abnormal arteriovenous communication were central to the site where the diastolic murmur and thrill were elicited. If the abnormal communication were thus centrally situated, compression of the brachial or radial and ulnar arteries would favor diastolic backward flow of blood toward the site of leakage, and would intensify the diastolic murmur and thrill. However, when the brachial artery was occluded by digital compression while a second observer applied a stethoscope over the subclavian vessels, the diastolic and systolic murmurs and thrills over the latter vessels completely disappeared. Digital compression of the radial artery alone or of the ulnar artery alone conspicuously diminished the murmurs and thrills, but these signs did not disappear until both vessels were occluded simultaneously. Application of pressure over the lower ends of the radius and ulna by means of the blood pressure cuff likewise effected the disappearance of the murmurs and thrills over the subclavian and brachial vessels.

The degree of compression necessary to cause disappearance of Duroziez' sign was tested by applying the blood pressure cuff to the middle of the forearm and placing the stethoscope over the brachial artery in the antecubital space. As the pressure within the cuff was raised, conspicuous diminution of Duroziez' sign occurred at 52 mm. of mercury; complete disappearance occurred at 58 mm. of mercury.

We were therefore forced to the somewhat surprising conclusion that both the systolic and diastolic murmurs and the thrills over the subclavian, brachial, radial and ulnar vessels were due to abnormally increased forward blood flow not only during systole but also during diastole, and that the increased blood flow occurred mainly because of abnormally dilated communications between the arteries and the veins about the wrist and the hand.

The pathologic physiology of Duroziez' sign has been studied in a variety of conditions, and its importance in differentiating aortic regurgitation from other conditions with similar peripheral phenomena will be the subject of a communication in the near future.

SUMMARY AND CONCLUSIONS

1. A case of hemiangiectatic hypertrophy and congenital phlebarteriectasis has been studied clinically. As a result of the observations made, criteria for the diagnosis of the condition have been established.

2. The left arm was conspicuously larger than the right; the blood flow through the left upper extremity was considerably increased, but the volume output of blood per minute from the heart and the velocity

of blood flow through the lungs were normal. The velocity of blood flow in the left arm was far greater than that in the right arm.

3. The so-called diagnostic signs of arteriovenous aneurysm are not diagnostic of arteriovenous aneurysm, but are rather to be regarded as signs of free arteriovenous communication; the exact nature and site of the communication must be determined by further study.

4. The following signs may be regarded as manifestations of free artery to vein communication; they do not denote whether the artery and vein communicate by direct anastomosis or by intermediate vascular plexuses: (*a*) increase in pulse pressure in the affected part due to elevation in the systolic and reduction in the diastolic blood pressure; (*b*) lowering of the general diastolic arterial pressure of the body; (*c*) increase in venous pressure in the affected veins and their tributaries without the general venous pressure of the body necessarily being affected; (*d*) capillary pulsation; (*e*) raised ventricular rate; (*f*) normal or increased output of blood from the heart; (*g*) normal or increased size of the heart; (*h*) abnormally high oxygen content of the venous blood of the affected part; (*i*) elevation in the temperature of the skin of the region in which the abnormal communication is situated, and (*j*) thrills and murmurs over the site of the abnormal communication and over the arteries leading to the lesion.

5. If after an artery is occluded the ventricular rate slows, the general diastolic blood pressure of the body rises, a lessening of venous engorgement of the affected part occurs, and the peripheral murmurs and thrills disappear, the abnormal artery to vein leakage lies in the segment of artery compressed or in its peripheral continuation.

6. The signs of multiple free communications characteristic of hemangiectatic hypertrophy and congenital phlebarteriectasis that distinguish this condition from the direct anastomosis of arteriovenous aneurysm are as follows:

(*a*) There are usually several or numerous dilated arteries leading to the site of phlebarteriectasis; there is generally but one dilated arterial trunk leading to an arteriovenous aneurysm.

(*b*) Systolic venous pulsations are transmitted away from the periphery in congenital phlebarteriectasis; they are transmitted toward the periphery as well as centrally in arteriovenous aneurysm.

(*c*) Increased growth of the region in which the abnormal communications are situated favors the diagnosis of phlebarteriectasis rather than arteriovenous aneurysm.

THE MAN-ENVIRONMENT UNIT AND PEPTIC ULCER*

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Natural historians have always insisted that it is impossible to think of a living creature apart from its environment. Indeed, the two are so intimately joined that it is no easy task to decide, for example, at what stage oxygen from the surrounding air fuses as oxyhemoglobin with the structure of the organism, or when ingested carbohydrate becomes vitalized in the energy productions of muscle. Consequently, the investigation of a human being's constitution must include all the gross and subtle details of his environment—it becomes in effect a study of the "man-environment unit." The problem would perhaps be easier if the palpable universe comprised man's only envelop. But because of his imaginative faculty, his phantasy life, another vast imponderable yet entirely personal universe supplies an equally complex and poignant environment to which he must likewise make adjustment. To the pressure of the physical world he responds in general with consciously directed muscles. Such muscles are chiefly concerned with the life of gross or spatial relation to environment. The other variety of muscle, nonstriated and not under conscious control, carries out the vital processes supporting the life of inner existence and procreation. But this type of contractile tissue is strongly influenced by emotions. Yet it is not necessary that the emotions be perceived in consciousness to be effective in modifying the function of organs equipped with smooth muscle. Ordinarily, if the organism is in good emotional equilibrium, the body machinery moves easily at its work, quite automatically and unnoticed by the individual. But if there is a disturbance, no matter how minute, of the balance between the human animal and either of its two universes, signs of that disturbance are immediately apparent. Consequently, we may accept the thesis that disease is simply the expression of maladjustment between organism and surroundings, an overthrow of the delicate structure termed the "man-environment unit."

Gastro-enterology, dealing with the stomach and intestines, is concerned with vital apparatus which is perhaps more than any other

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physiologic system exposed to blows from both ponderable and imponderable worlds. Physical, chemical and thermal onslaughts alternate with the rapid fire of emotions, such as fear, anger, jealousy and sexual confusions. Yet no two stomachs and no two intestinal tracts react similarly to any of these menaces. This is because the gastrointestinal tract is not the man; the whole man is the digestive mechanism, and as the whole man responds to the pressure of the whole environment, so will any of his parts respond—for each cell and system within him is stamped indelibly with his special mark. This special mark has been called the personality. It was for this reason, doubtless, that we found the peptic ulcer race so well adapted to our studies in constitution. The methods to which reference will be made and the descriptions, interpretations and conclusions are applicable in principle to the subjects of any illness. However, they are, in this communication, based on observations of what we have called the peptic ulcer race. We are aware that the use of the term race, with such a connotation, is unacceptable to some critics of the work. But if, in this connection, the word is deprived of its ethnological significance, it is at least etymologically and by derivation permissible.

While in our previous studies the plan of recording observations was carried out on the four panels of personality, anatomy, physiology, psychology and immunity, we have found it simpler for our present purpose to discuss the material under three headings, namely, genetic, anthropomorphic and anthropopsychic.

GENETIC STUDIES

The genetic studies have not been made primarily to display a disease tendency, but rather to uncover trends in the constitution of the family, just as they have been studied in the individual. With the emergence of the total personality as an essential factor in the causation of disease, it becomes increasingly necessary to observe the elements from which it arises. The physician cannot gain complete understanding of his patient if the more important aspects of the latter's heredity are omitted from the study. Often, also, the patient throws much light on his own psychologic patterns and conflicts as he discusses the members of his family, their traits and habits, their adjustment to environment and his relationship with them.

The hereditary influences play the basic rôle in the final determination of the man, his morphology, his psychology, his strengths and his weaknesses in all the systems of the body. But these inherent values are strongly conditioned by his surroundings. The finished individual, the phenotype, is therefore the up-to-the-moment resultant of the interplay between inherited qualities and the modifying influences from the world about him. For example, it might be imagined that four brothers of

the same fraternity have the same general inherited weakness of the gastro-intestinal tract. In number one, there is also a psychic instability, and the nervous response to slight stimuli may affect the visceral nervous system so adversely that he early finds himself incapacitated by ulcer of the stomach. Number two has a more stable nervous system and yet is subjected to the vicissitudes of life so forcibly that the deleterious effect is felt in the gastro-intestinal tract, though perhaps not so severely as in number one. Number three may have a poor nervous make-up, yet at the same time his adjustment to the environment may be so good that the weakness remains undisclosed. Number four may have both a good nervous system and environmental adaptation and, like number three, may remain well.

The genetic studies have embraced the following points: racial extraction, morphologic types, disease history, sex distribution and psychologic make-up. Such a graphic description of the family brings into much clearer relief the characteristics of the patient. In the disease and psychologic pattern the patient is often liable to project his own symptoms on the various members of the family, hence the necessity of interviewing other members besides the patient. Histories of thirty-two ulcer families and thirty-two gallbladder families have been used for this study. To draw conclusions from so small a series is obviously unwise. Yet the close approximation of our findings in respect to disease frequency and other studies of greater numbers gives confidence in the validity of the general trends displayed in the "family history." Naturally, disease overlappings are frequently found, and no family presents a homogeneous pattern. However, when these two groups of families are placed side by side, the differences stand out quite as clearly as do the differences in the individual patients of the two groups.

Sex Distribution.—The ulcer families are represented by 26 male patients and 6 female patients, and the gallbladder families by 5 male patients and 27 female patients. No sex selection was made in taking the histories, so long as the patient was able to give intelligent cooperation. In the members of the ulcer patient's immediate fraternity, a sex distribution in the ratio of 138 males to 100 females is found, while the gallbladder families present quite the opposite picture of 100 males to 130 females. There is, then, a tendency for the ulcer families to produce a preponderance of males and the gallbladder families a preponderance of females.

Morphology.—In general terms a description of the habitus of members of the family was elicited. The terms slender, medium, stocky and stout were employed. The ulcer families reported 75 per cent of the brothers and sisters of the patient as slender or medium build, while the gallbladder families reported 54 per cent of the immediate members of

the patient's fraternity as stocky or stout. Seventy per cent of the fathers of patients with ulcers were described as medium or slender build, and only 30 per cent as stocky or stout. Of the fathers of patients with gallbladder disease, 55 per cent were described as slender or medium and 45 per cent as stocky or stout. The mothers of patients with ulcers were reported as 55 per cent thin and 45 per cent stout, while just the opposite picture was found among the mothers of patients with gallbladder diseases, with 55 per cent stocky and 45 per cent thin. The findings show that the slender and the medium build are in the majority in the ulcer families and the stocky or stout in the majority in the gallbladder families.

Disease Incidence.—Peptic ulcer was found in 6 families; indefinite stomach trouble occurred in 13 additional families and cancer of the gastrointestinal tract in another family, a total of 20, or 62 per cent, with a heredofamilial weakness of the gastro-intestinal tract. Ruhmann [1] found 48 per cent of 50 families with a similar hereditary history; Aschner [2] found 65.3 per cent and Spiegle [3] found 61 per cent. Aschner reported that 15 per cent of the families of healthy persons gave such a history, Spiegle reported 15.5 per cent. Assuming that there is a hereditary influence, the tendency is in the form of a pathologic inferiority of the gastro-intestinal tract.

Ruhmann [1] pointed out that definite ulcer is more frequent among the sibs and descendants of the patient, and indefinite stomach trouble is commoner among the ascendents. The question arises as to the possibility that this fact may be due to more refined diagnosis nowadays and the closer familiarity of the patient with his own and the succeeding generation. Aschner [2] concluded from her studies of 120 ulcer families that the gene for stomach inferiority is a recessive, but is not sex-linked. She found that in cases in which both parents were affected, 50 per cent of the offspring were also affected. If one parent is sick and the other has a sick heredity, 25 per cent of the offspring are affected. If both parents are well but show a sick heredity, 10 per cent of the offspring are affected. The small number of families comprising our series hardly permits of such an analysis. After working over a long period with patients with ulcer, we have found it hard to conceive that a specific gene weakness is responsible for so complicated a disturbance of the vegetative nervous system as that which results

1. Ruhmann, W.: Der Ulcuskranke: Studien zur Konstitution und Symptomatik am gesamten Status bei chronischen Ulcus pepticum mit besonderer Berücksichtigung des vegetativen Nervensystems, Berlin, S. Karger, 1926.

2. Aschner, B.: Ueber Konstitution und Vererbung bei Ulcus ventriculi und duodeni, Ztschr. f. d. ges. Anat. **9**:6, 1923.

3. Spiegle, E.: Deutsches Arch. f. klin. Med. **126**:45, 1918.

in lesions of the gastro-intestinal tract. Nor can we accept the condition as a recessive mendelian phenomenon in view of the variability of the external influences that may determine its expression.

Among the immediate members of the patient's fraternity, our studies show that 3.5 males to 1 female express gastro-intestinal weakness, exclusive of the patient. The mothers show the condition twice as often as do the fathers. Seven families gave a history of such weakness among the maternal collaterals and only one among the paternal collaterals. In this connection it should be stated that the maternal line is frequently better known to the patient than the paternal line. In all except one case the relatives with gastric symptoms were described as of slender or medium build. The gallbladder families show that in the members of the patient's fraternity, exclusive of the patient, indefinite digestive disturbances are three times more frequent in females than males. The condition occurs with about equal frequency in the paternal and maternal lines.

Tuberculosis was found in twelve ulcer families, or 37 per cent. Ruhmann [1] reported a 30 per cent incidence in his fifty families. The condition occurred twice as frequently in males as in females. Pneumonia was reported in 50 per cent of the ulcer families, and again this condition was found to be twice as frequent in males as in females. When it is recalled that the ulcer families are represented by twenty-six males and six females, the preponderance of male susceptibility to diseases within the zone of the pneumogastric nerve in these families is interesting.

Asthma occurred in eight, or 25 per cent, of both the ulcer and the gallbladder families. Diabetes occurred in only two ulcer families, as compared to seven gallbladder families. Gallstones were reported in two ulcer families; a mother was the subject in each case. This gives a gallstone incidence of 6 per cent as compared to 8 per cent found by Ruhmann.[1] The gallbladder families reported eleven cases, or 34 per cent of gallstone. No cases of goiter were reported among the ulcer families, while the gallbladder families reported four cases. Arthritis was found in one ulcer family and in three gallbladder families.

Psychologic Make-Up.—The study of the psychologic make-up of the families offers many difficulties. To extract from a patient a picture of the colorless personality of a brother, for example, is often an almost impossible task. Yet something may be gained from direct questioning about his schooling, occupation, stability in work, marriage, hobbies, interests and his reaction to any specific situation with which he would be likely to come in contact. To present this phase of the study statistically is obviously impossible. However, a perusal of sev-

eral selected histories will doubtless go far to show how strongly personality patterns are imprinted in the family.

Schematic patterns of the families of the patients in the four cases in which analytic histories are given in this paper will be presented. They will be found in the anthropopsychic chapter together with the case histories. The charts display the main outlines of personality which are most typical and most often found in the ulcer families. Also, the disease display and morphologic aspects of the family members are noted.

Summary.—The genetic studies may be summarized as follows:

1. There is a tendency for the ulcer families to produce a preponderance of males and the gallbladder families a preponderance of females.

2. Patients with ulcers are of families in which the long thin type predominates as contrasted to the gallbladder families in which the short thick type is in the majority.

3. There is definite evidence in the ulcer families of a heredofamilial weakness of the gastro-intestinal tract, 62 per cent of the families reporting such a history.

4. Gastro-intestinal weakness is three and one-half times more frequent among males than among females in these families, and almost without exception it is found in thin people. Males of these families are also much less resistant to other diseases in the zone of the pneumogastric nerve (tuberculosis and pneumonia) than are females.

5. Diseases of a catabolic nature occur more frequently in ulcer families, and anabolic disease more frequently in gallbladder families.

ANTHROPOMORPHIC STUDIES

The literature on peptic ulcer is filled with references and descriptions of the body build of such sufferers. There is general agreement that they belong to the so-called asthenic type. But, at this point, we must take exception to the use of the terms sthenic and asthenic, originally introduced by Stiller [4] to describe certain inadequate human beings. Sthenic, from the Greek *σθένος*, means strength, and when used of man or animal connotes an energy producer. The term sthenic has, of late, been loosely used to signify the short thick-set type originally described by Hippocrates, just as its opposite, asthenic, is now applied to the long, thin variety. Now, so far as intensity and, indeed, duration of energy production are concerned, long slender people often surpass the thick-set. It is consequently misleading to designate mor-

4. Stiller, B.: Die asthenische Konstitutionskrankheit, Stuttgart, Ferdinand Enke, 1907.

phology by a word that indicates physiologic quality. However, the term asthenic in this instance has been linked with the slender individual whose ponderal index (that is, the height-weight ratio) is consistently low. Aschner,[2] in a most comprehensive study of the subject, concluded that there is no typical ulcer habitus. Our observations do not support this finding; indeed they clearly envisage not only a physical and psychic type subject to this disease, but one so well defined that it is possible, almost without error, to determine from the individual's constitution whether the location of the ulcer is gastric or duodenal. The differences will be discussed later. Also in disagreement with Aschner, both Tscherning [5] and Ruhmann [4] expressed the belief that patients with ulcers are found chiefly in the ranks of the linear types, with certain admixtures of the lateral. According to our observations, derived by both anthropometry and anthroposcopy from 125 cases, the peptic ulcer race is definitely composed of the linear, rather than the lateral, type of person. However, while they are slender and, even in good health, presenting a consistently low ponderal index, they cannot properly be called asthenic. On the contrary, unless seriously depleted by the disease, they display an astounding amount of swiftly liberated, and often sustained, nervous force. This produces in many of them that quality of quick physical elasticity which bespeaks a high energy potential. Such an impression naturally gains vividness and color from the state of psychic or emotional tension. This aspect of the total personality will be dealt with later.

The facial design of members of the ulcer race is not so different from that of the general run of humanity as to make at first a striking impression. Yet when one has become familiar with its detailed characteristics, it is not difficult to recognize. In general, this face is broader in its upper half and tends to taper, rather sharply, to a small pointed chin. The eyes are separated by an interpupillary distance of from 60 to 62 mm., which is the average for the general population. But the relation between the interpupillary space and the facial diameter is the most satisfactory from the standpoint of appearance of all the disease groups. The eyes are neither too close together nor too far apart. The palpebral fissure is consistently wide, often enough to show the sclera above the iris. This character is especially interesting in view of other evidences of tension of the vegetative nervous system, which will be referred to subsequently. It doubtless accounts for the alert, watchful expression, which conveys a suggestion of continual apprehension mixed with defiance, common to the ulcer type when the person is in good health. But when the gastric symptoms are

5. Tscherning, R.: Ueber die somatische und psychische Konstitution bei Ulcus ventriculi, Arch. f. Verdauungskr. **31**:351, 1923.

severe and the whole organism is reduced from the effects of indigestion and scant diet, then the wide eye slit produces the characteristic expression of exhaustion and despair with which every one is familiar. The defiant note has gone.

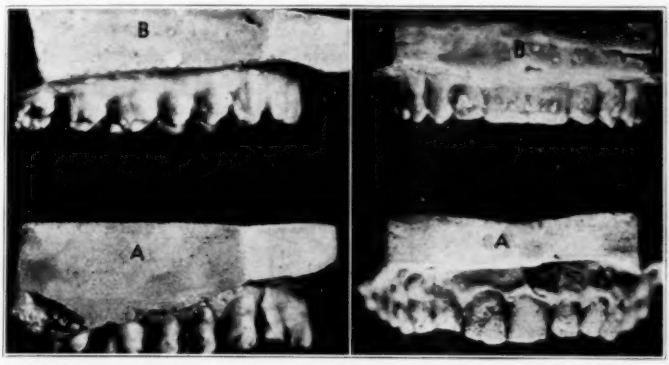

Fig. 1.—Lateral and front view of the upper jaw: *A*, ulcer; labial version of incisors and curving occlusion; *B*, gallbladder; vertical or lingual version. Straight occlusion. (From Draper, G.; Dunn, H. L., and Seegal, D.: Studies in Human Constitution, J. A. M. A. **82**:431 [Feb. 9] 1924.)

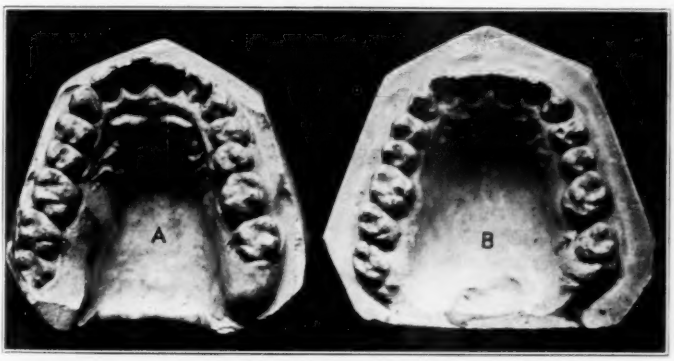

Fig. 2.—Palate view of the upper jaw: *A*, ulcer; pointed incisor arch, deep palate, forward slanting incisors; *B*, gallbladder; flat incisor arch, shallow palate, vertical insertion of incisors. (From Draper, Dunn and Seegal.)

Although the lower part of the face in general tends to be smaller than the upper, it presents significant details of structure in both the upper and the lower jaw. The dental ridge (figs. 1 and 2) usually forms a U-shaped oval, and the vertical cross-section of the hard palate

shows an arch of similar design. The incisor teeth extend in slight labial version from the anterior alveolar margin. From this, the palatal arch sweeps up and back in a low slanting curve to the deepest part of the vault almost at the posterior edge of the bone. The teeth themselves are usually of clear pearly quality. The lateral incisors are definitely narrower than the central, the biting edge is sharp, and the profile curve of the bite line is waving, with low points at the molars and incisors. In the lower jaw (fig. 3), the gonial angle (formed by the intersection of the posterior border of the ascending and the lower border of the horizontal rami) averages 124 degrees, which falls well within the range for the general population (from 118 to 127 degrees). Clearly, then, this character is not significant in respect of the general population. But it gains immediate interdisease group significance when compared with the 115 degree angle of the gallbladder people, and the

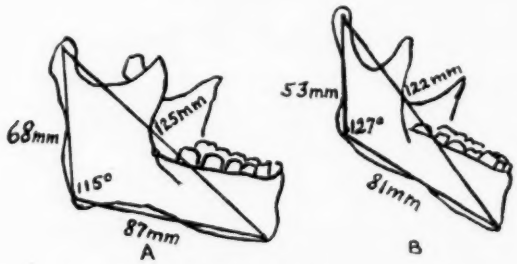

Fig. 3.—Diagram of the jaw types from the gallbladder (*A*) and the gastric ulcer (*B*) race. (Reproduced by courtesy of the Williams & Wilkins Company, Baltimore.)

130 degree angle of the people with acute rheumatism. The following tabulation shows some of the more important interdisease differences.

	Peptic Ulcer Mean	Gallbladder Mean	Range for General Population
Ponderal index	32.2	44.0	33.41
Gonial angle	122.5°	115.0°	118-127°
Subcostal angle	44.5°	62.0°	35-60°
Anterior index upper jaw	54.0	58.0	
Anterior posterior chest diameter	200.0	222.0	190-220
Anterior posterior diameter/chest length index	58.8	66.8	58-66
Lateral incisor/central incisor index	75.0	89.0	78-94
Hand index	45.8	47.2	44-48

From the standpoint of anthropometry, the significant features of the trunk and extremities are the somewhat low anterior posterior diameter-chest length index, narrow subcostal angle, relatively short arms and eunuchoidal trunk-extremity ratio. The hands are slender and long fingered, and the nails are narrow, long and laterally curved, and in the gastric group often display well marked lunulae. At this point it may be well to say that the duodenal cases present in general the same morphology, but almost every detail is slightly heavier or coarser. The trunk is thicker set, the subcostal angle is not so consistently narrow, and the extremities are less lanky and eunuchoidal.

Fig. 4.—*A*, face view of a man with a duodenal ulcer. *B*, face view of a man with a gastric ulcer.

The hands are not so gracile, and the nails are flatter and squarer and show smaller or absent lunulae. The pilous system is usually not very strongly developed in either group. Though, in the males, the hair distribution follows generally the so-called masculine distribution, lightness of growth and occasional absences occur in zones that are characteristically bare in the female. The facial hair is almost always vigorous and abundant, especially in the gastric group. But in addition to the suggestion conveyed through the body hair, the body form displays numerous other subtle indications of this emphasis of the female component in the androgynous mosaic of these patients. Among these may be mentioned slightly sloping shoulders, more marked in the duodenal group, short arms and fulness over the trochanter region and

above the gluteal masses and the curve of the outer margin of the leg below the knee (figs. 4 and 5).

There are a few instances in which both peptic ulcer and cholelithiasis occur in the same person. St. John [6] reported 13 in a series

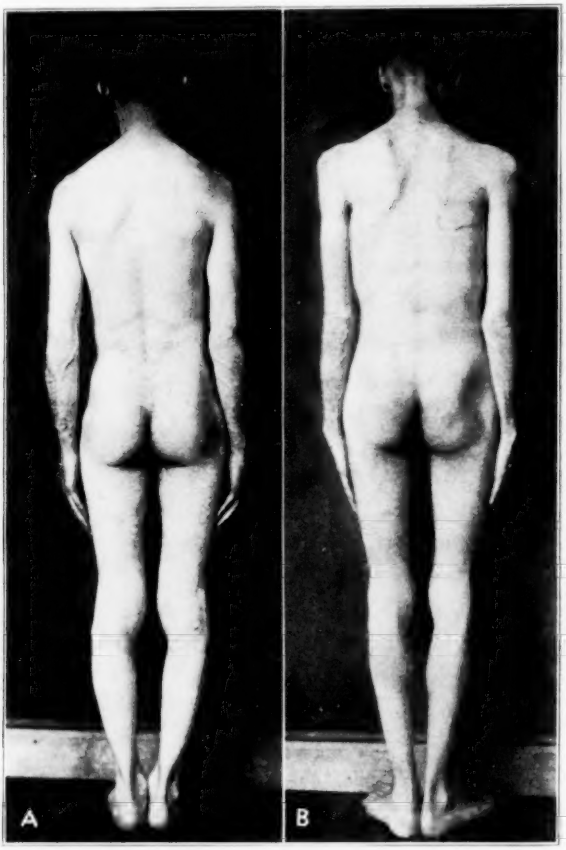

Fig. 5.—*A*, back view of a man with a duodenal ulcer. *B*, back view of a man with a gastric ulcer.

of 490 peptic ulcers. Of these 13, the ulcer was duodenal in 11 cases, pyloric in 1 and gastric in 1 instance. The 1 case in our series conformed morphologically to the other members of the uncomplicated duodenal group.

6. St. John, F. B.: Unpublished report.

ANTHROPOPSYCHIC STUDIES

In our previous studies [7] of the psychologic panel, the chief emphasis seemed to fall on the exaggerated fear sense in the peptic ulcer race. The motor and psychomotor activity was found to be unusually high, and the patients were prone to swift and intense excitability. Their capacity for long-sustained effort is not great; they are of those whose intense activity is intermittent, because they are easily fatigued. Still they recover their energy promptly after short rest periods and the frequent ingestion of food. The direction of their interest and attention is generally outward; classic extroverts, who engage busily with the passing show. Beneath an outward manner of assurance, ready to

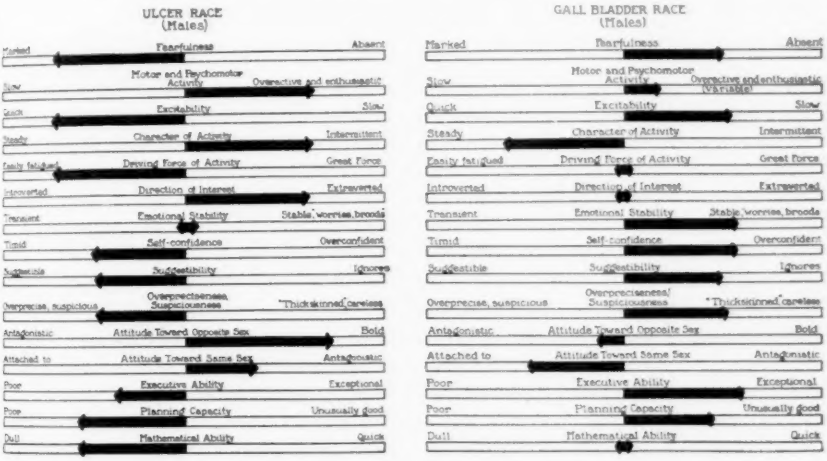

Fig. 6.—Psychologic panels

seize any opportunity which offers, there is a latent timidity. This may be one cause at least for their tendency to overpreciseness in all they do and to be suspicious of people and situations. They are easily suggestible. In their relation to the opposite sex, the males are bold and eager and display an exaggerated heterosexual interest. Conversely, they show signs of antagonism toward their own sex. The females, on the other hand, have definitely diminished interest in erotic experience. All the orderly, more logical qualities, such as planning capacity and executive and mathematical ability, are not naturally highly developed in these mercurial people. Often, however, by a powerful compensatory effort they succeed in schooling themselves in executive work (figs. 6 and 7).

7. Draper, G., and McGraw, R.: Studies in Human Constitution: V. The Psychological Panel, Am. J. M. Sc. **174**:299, 1927.

In our original interpretation of the total personality of the peptic ulcer individual, we concluded that both on morphologic and on psychologic grounds, maleness was the essential feature. Apparently this thesis was further supported by the statistics of sex incidence of the disease. It is true that some observers report more female cases than male, and that today in Germany peptic ulcer is believed to be more frequent in females than in males. However, more recent publications undoubtedly give precedence to men. Thus, St. John [6] reported in a series of 281 duodenal ulcers a sex ratio of 9 males to 2 females; among 87 pyloric ulcers, 5 males to 3 females and among 104 gastric ulcers, 3 males to 2 females. A further reference to this descending ratio will be made later.

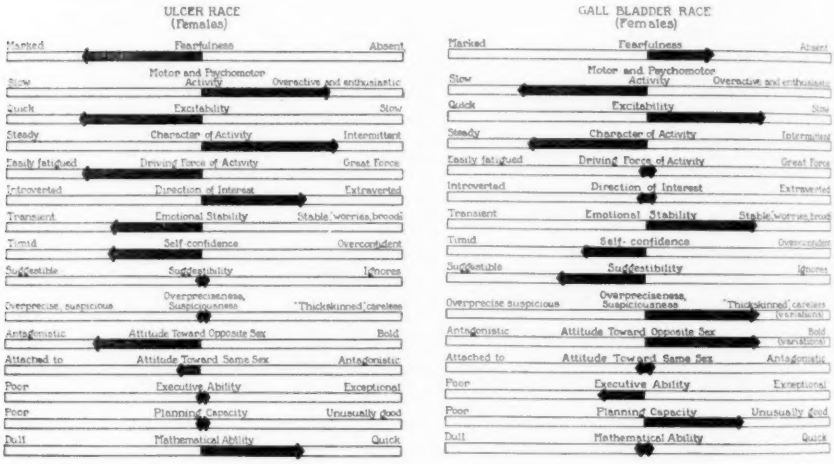

Fig. 7.—Psychologic panels.

Recently, however, while reading Crile's [8] paper on the subject of recurrent hyperthyroidism and recurrent peptic ulcer, certain questions arose concerning the validity of the male disease thesis which we have heretofore held. In that communication Crile pointed out that 60 per cent of patients with hyperthyroidism have digestive disturbances. He further called attention to the similarity of evidence of vegetative nervous system disturbance found both in patients with exophthalmic goiter and in those with peptic ulcer. Among these patients, for example, were widening of the palpebral fissure, fatigue, decrease of tissue and body fluid p_H, sweating palms and the subjective feelings

8. Crile, G. W.: Recurrent Hyperthyroidism; Recurrent Peptic Ulcer, Proc. Inter-State Post-Grad. M. Assemb., North America, October, 1929, p. 355.

of nervousness. He was able to show that when myxedema was produced, the acidity diminished. In five cases of peptic ulcer which had resisted medical and surgical treatment, he further demonstrated by resection of the left suprarenal gland and part of the thyroid, that the acidity could be reduced to normal. In addition to these observations of Crile, it is commonly known that exophthalmic goiter and hyperthyroidism are from six to eight times more frequent in women than in men. Similar suggestions are found in Simnitsky's [9] work on the sympathetic nervous system. In view of these considerations, consequently, it would appear paradoxical that more men than women should be affected with ulcer. The only explanation for this paradox seemed to be in the fact of femaleness within the male.

This disclosure led us to reexamine the literature and our own case histories and observations. We soon began to see the evidences of emphasis on the feminine character of body build which have been referred to, and further to discover in the psychologic structure similar but more marked and important characters. The violent impetuous behavior that we had viewed objectively and supposed to be the demonstration of virility, on deeper psychologic investigation, turned out to be of quite a different nature. In the earlier literature on this subject of peptic ulcer, there are indications that a highly sensitive, feminine quality of temperament was recognized by certain observers. Thus, Gilles de la Tourette [10] not only gathered statistics which showed in one series a ratio of 2 males to 1 female and in another series 1 male to 4 females, but in addition pointed out that there was a strong hysterical trend in the patients with ulcer and emphasized as a possible cause of ulcer the well known vasomotor and trophic disturbances of hysteria. Charcot [11] likewise suggested that the "crise noir" or vomiting of blood might sometimes be hysterical. In referring to this point nearly fifty years later, von Bergmann [12] declared that an ulcer often hides behind the "crise noir" of Charcot. This same author, summing up the now generally accepted belief that a strong emotional factor contributes to the cause of ulcer, pleaded for the most finely drawn anamnesis and what he termed the "subtile diagnose." He urged physicians not to be misled by the stolid mien of the Holsteiner beneath which the tension of emotional conflict may be terrific.

9. Simnitsky, S.: Weitere Beobachtungen zur Frage über die Bedeutung des Milieus in der Pathogenese der peptischen Geschwüre, Klin. Wchnschr. **6**:991, 1927.

10. de la Tourette, Gilles: L'ulcère ronde et hysterie, Semaine méd. **19**:377, 1899.

11. Charcot, J. M.: Leçons du mardi à la Salpêtrière, Paris, E. Lecrosnier & Babé, 1889, vol. 2, pp. 272 and 342.

12. von Bergmann, G.: Die nervösen Erkrankungen des Magens, Verhandl d. Gesellsch. f. inn. Med., 1924, Kongr. 36, p. 168.

But it is the nature of this conflict that has interested us especially during the past two or three years. That fear is clearly an important element there is no doubt. Yet it is not always easy to connect a conscious fear with the gastric symptoms. Not infrequently, of course, an acute fear episode is closely associated with a violent gastric attack, hemorrhage or even perforation. Nevertheless, there is good reason to believe that the original formation of the ulcer occurred a long while before one of these serious events. Fear has not been recognized consciously, however, in the earlier stages of the malady, and, indeed, is usually denied vigorously by the patient. This situation is well illustrated by the case one of us reported last year of the public official whose hemorrhage occurred following a narrow escape from death by collision with a railroad train. This patient's ulcer had existed for some time prior to that nearly fatal event; its formation was related to his childhood and adolescent fear of humiliation because of unsuccessful competition with his younger brothers. Later on, after two years without symptoms and a continuous diminution in the size of the crater, as shown by roentgenograms, gastric symptoms returned temporarily when a fellow passenger at sea died, in a few hours, of perforation.

In other words, there seem to be two separate and independent sources of fear. One of these is subconscious and unrecognized by the patient. The anxiety that arises from this level has been at work over a long period. The other, consciously perceived, is formed by the menacing episode that threatens life, limb or ego. The former more chronic element of this double fear attack has engaged our interest, especially of late, because it appears to be almost part of the constitution itself.

In this connection it is of interest to refer to the work of Cannon [13] on the autonomic nervous system. He remarked in his "Linacre Lecture":

> Not only states of the external environment itself, but responses of the organism to situations in the external environment, are associated with disturbances of the internal environment. This personal, individual climate, which we carry about with us, must not change if we are to continue to be effective. In order that the constancy of the internal environment may be assured, therefore, every considerable change in the outer world and every considerable move in relation to the outer world, must be attended by a rectifying process in the hidden world of the organism. The chief agency of this rectifying process, as we have just noted in many illustrations, is the sympathetic division of the autonomic nervous system.

Cannon further pointed out that animals deprived of the sympathetic nervous system can survive successfully within a protected environment provided by a quiet laboratory, but when such animals

13. Cannon, W. B.: The Linacre Lecture on the Autonomic Nervous System, London, Cambridge University Press, 1930.

are forced to meet any struggle with temperature changes, muscular activity or emotion they promptly show failing function of all viscera equipped with smooth muscle.

The gastric disturbance in cases of peptic ulcer in man, as well as the other signs of sympathetic nervous system weakness (e. g., sweating, fatigue and wide palpebral fissures), forms a picture highly reminiscent of the sympathectomized animals. It would seem that these peptic ulcer people possess an inadequate sympathetic nervous system. This inadequacy may be the result either of an inherited weakness or of a wearing out process. The latter might well follow prolonged exposure to the chronic anxiety state just referred to. It is the nature of this anxiety that we propose to discuss later in the section dealing with the androgynous mosaic.

In order to demonstrate the subtle indications of the feminine component in the personality, the following psychologic histories are presented. Most of them are nonanalytic, and their objective nature makes it somewhat difficult to interpret them from an analytic point of view, yet their significance is quite apparent. We have made about sixty of these studies in all. From these, nine complete histories and fifteen excerpts have been selected for presentation.

It is not easy to gain access to the storehouse of a human being's emotional life; the intimate details of events that involve feelings and loyalties are jealously guarded. For this reason direct questions, or even leading ones, are invariably met at first with silence or negative response. Only when a friendly and dependable confidence has been established between patient and physician do the significant contents of the former's secret thought chamber appear. Much of this is unavailable to the too abrupt questioner, not because it is lost in the patient's subconscious mind, but because it is withheld for reasons of fear, loyalty or sensitiveness to tactlessness on the physician's part. When the proper relationship has been established, the concealed thoughts and later the subconscious residues will begin to distil over, hesitatingly at first and later sometimes with a gush that may in itself have a healing as well as a diagnostic value.

REPORT OF CASES

CASE 1.—*Duodenal Ulcer.*—This patient, T. D., was 34 years old and unmarried. He was of the classic ulcer type, with wide palpebral fissures, moist palms and chronic fatigue. An operation for duodenal ulcer was performed five years before consultation, and since then he had been under almost continual treatment for gastric distress. He came of New England stock, but his family moved to Texas shortly after his birth and he had lived there ever since. The circumstances of his birth were important. Shortly after he was conceived his father left home for no apparent reason and was not heard from again until the patient was 12 years old. During his early childhood, the boy frequently had the feeling that he was an

unwanted addition to the family. Furthermore, the mother was so occupied with her efforts to support the family that he saw little of her. He had two older brothers and two older sisters, one of whom had played the part of mother to him in his early years. Added to the feeling of insecurity which this parental lack produced was the quality of effeminancy which the boy himself recognized in his own personality. On this account, he became the butt of his playmates' ridicule. To compensate for, or to obliterate, these feminine traits, he consciously strove to develop masculine attitudes and behavior. He succeeded in this so well that people now often discuss the subject of effeminate men with him. "Of course they wouldn't do this," he went on, "if they suspected that I was like that." Furthermore, he had done well in business and by great determination had become the driving executive head of an important department of a large manufacturing business. He did not by nature possess ability or interest in executive work.

When he came to the Constitution Clinic, after five years of intermittent recurrences since his operation, he said that he was now convinced that his trouble was primarily nervous or mental. With great difficulty and resistance, although he had brought himself voluntarily to the task, he finally stated that he feared that he was homosexually inclined. Further inquiry, however, soon revealed that he had never had any actual sex experience with members of his own sex, and only very incomplete attempts with women. He remarked that his training in this phase of life had been one of stern puritanical repression, ignorance and fear. At the age of 10 he had become attached to the little daughter of the minister of the local Baptist church and subsequently became an ardent church-goer, largely, he thought, because it kept him in close association with the little girl. This attachment lasted until he was 17 or 18 years of age. At that time, he chanced to go to a service in a church of another denomination where he saw a young acolyte of great personal beauty. For the next few years he continued to be a most devoted attendant at the services in this church. He never met or spoke to the acolyte whom he held continually in his mind.

Six years previous to examination he fell in love with a woman who was self-supporting and earning an income considerably larger than his own. Their relationship advanced rapidly and intensely until sexual activities had almost reached the stage of intercourse. But at this point the patient was checked by the traditions of his ancestors and the teachings of his two churches. Marriage alone, by sanctification, could permit the final sexual act. On the other hand, if he married this woman whose earned income was quite adequate to support them both, though his was not, he would find himself in the humiliating position of a dependent on his wife. This was more than his already overtaxed masculine component could tolerate. In the face of this dilemma, he terminated the relationship abruptly. During the ensuing months, he sought a solution of this problem and finally attempted one by an effort which he said was purely rationalized and quite without an emotional conviction. He asked the woman to live with him, unmarried. This gesture was promptly and vigorously repudiated by the woman, and he retreated more than ever depressed over his defeat in life. Within a few months after this episode, his stomach symptoms began and grew increasingly worse until the operation was done.

During the course of work at the clinic, while the patient still believed himself to be homosexual, he had two interesting dreams in rapid succession. In the first, he ascended the stairs to his bedroom and, outside the door, he saw his two nephews, sitting at each end of a sofa, curled up in the attitude of fetuses. He walked past these without stopping, entered his room and closed the door. Within, he found his sister, who promptly changed into the girl he was somewhat interested in at

the time. He made amorous advances toward her, which terminated in an emission. The associations with this dream are significant. The nephews, who appeared as infants, were actually full grown youths for whom he the patient had felt the possibility of homosexual attraction. The sister was the one who had played the rôle of mother to him.

In the second dream he entered a house with a push button entrance. Three names were in the list beside the bells. On the first floor was a count, on the second a prince and on the top the girl he was going to visit. His eye ran up the list, past count and prince, and without hesitation he pressed the bell of the lady's apartment. He started up the stairs and met many obstructions in the hall, composed of furniture. Finally he reached the girl's room, entered and found her lying partially clad on the bed. He again made amorous advances which concluded with an emission. The association brought out the immediate linking of count and prince with homosexuality. The obstructions were related to his traditions and the belief that he was unable to achieve a normal sexual life.

Two days after these dreams the patient complained of a return of his gastric discomfort. It was during the discussion of these symptoms and the preceding dreams that the patient brought out the account of the early attachment to the pastor's daughter, the acolyte and the love affair that was broken off before the original onset of the stomach symptoms. On the basis of the foregoing history, the patient explained the return of his indigestion in the following way: "It would seem that the phantasy love affairs with the parson's daughter and the acolyte were sanctified by my devotions in the two churches. But the later love episode, in which marriage was impossible because of the blow to masculine pride, lacked the sanctification by the church and led to ulcer formation. Now the recent dreams which display a phantasy sex fulfilment, unsanctified by marriage, have presented in phantasy (dream life) the same situation which existed in reality before the original ulcer."

Following the conference in which this piece of insight developed, the stomach symptoms receded and have not reappeared.

Analysis of Family History.—On the maternal side of the family, the women were replete with forcible qualities of personality. The mother and two sisters of the mother were women of marked executive ability and were quite capable of assuming the rôle as heads of the family. The maternal uncle was a chronic inebriate, lacked stability and definiteness of purpose, and showed little backbone in dealing with a domineering wife.

The patient's father was apparently more attached to his mother and sibs than to his own family and chose to desert his wife and children and reestablish himself in the household of his mother. He had unusual manual dexterity but little business ability and courage.

The absence of the influence of the father in the home seemed to express itself in the fact that both of the patient's sisters married their employers. In neither case was the marital adjustment good. Possibly, too, the absence of the father in the home helped in determining the patient's sense of insecurity. Very early he felt the sting that he was an added burden to the family at a time when the father left the total responsibility to the mother. The brothers showed the mother influence in their marriages. The older one married a nurse; the mother was also a nurse. His wife continued in her professional rôle. He showed a marked feeling of insecurity and lack of stability in work. The second brother married a woman older than himself and brought her to the family home in preference to establishing a home of his own.

Schematic Pattern of Patient's Family History

CASE 1.—*Racial Extraction:* Paternal, unknown; maternal, American, English extraction.

I. No information regarding father's family.

Patient's Father

Medium build. Living, 75 years. Healthy except for occasional heart attacks past few years.

Deserted wife and children when wife refused to live with his family. Has never shown any sense of responsibility to family. Adventurer. Jovial, good mixer. Craftsman, cabinet maker. Marked manual dexterity but no obvious artistic sense. Usually lives alone and appears happy. Poor business ability.

Patient's Mother

Tall — muscular. Living, 75 years. Rheumatoid arthritis past years. Long history of chronic indigestion.

Good manager and successfully played man's rôle in the home. Never bitter against husband, though she made several futile attempts to engineer his return. Protective, conservative, self-confident, executive. Midwife—obstetric nurse. Out of home greater part of the time. Married at 25 years.

M. Sister

D'ed in 60's. Cancer of stomach.

Good executive, managed husband's business entirely. Severe, domineering, masculine woman, interested in men's work. Two children. Children usually lived with relatives.

M. Sister

Died in 70's. Rheumatoid arthritis.

Strong personality, domineering, outspoken, good business manager. Little feminine charm. Masculine appearance. Two children.

M. Brother

Tall, slender. Chronic alcoholism.

Violent and destructive when drinking. Claimed that he drank to escape a domineering and nagging wife. Cooper by trade. Good worker but lacked stability and ambition.

M. Brother and Sister

Both died in late 20's of tuberculosis of the lungs.

Sister

Medium height, slender. Meningitis at 3 years. Crippled from this. Died at 34 years. Cancer of stomach (after operation).

Sensitive, quiet, retiring. Self-conscious of lameness. Easily led, suggestible. Bookkeeper. Married at 30 years to employer—forced marriage because of pregnancy. Marital adaptation poor. Two children. One child a moron.

Brother

Five feet, 9 inches; medium build. Acute appendix at 35 years. Lived to 45 years. Health good.

Impulsive, self-assertive, domineering. Full of new ideas, political, etc. Talks much but never acts. "Blows with the wind." Suspicious, nagging, bitter toward life. Good machinist, but is constantly changing line of work. Opportunist, little foresight. Married at 35 years. Wife a trained nurse who runs a convalescent home. Three healthy children.

Sister

Tall; medium build. Health good.

Even tempered, well balanced individual. Acts with initiative. Plans well. Teaches bridge and other games at present to supplement the income. Married at 21 years to employer who was 10 years older. Husband an erratic business man who showed excellent possibilities before marriage. Two children.

Brother

Six feet; well built. Chronic catarrh as a child. Kidney inflammation recently.

Reticent, retiring, poor mixer. Usually alone as a child. Talks little. No spark or life—colorless. Introspective, introverted. Easily hurt but never expresses feelings. Married in 30's to girl older than himself. Never showed much interest in girls. Grocery store manager for past 20 years. Changes jobs occasionally but does not improve his position.

Brother

Died young, 3 or 4 years of age, of "dropsy."

Patient

Case 1
Duodenal ulcer.

The presence of a hereditary inferiority in the gastro-intestinal tract was also expressed. The mother gave a history of gastric disturbances. One of the mother's sisters and also the patient's oldest sister died of cancer of the stomach. Two cases of tuberculosis in the mother's family were also worthy of note.

All members of the family seemed to be of the long thin variety.

CASE 2.—*Duodenal Ulcer* (*P.O.*[13a]).—The patient, A. E., was 37 years of age He was morphologically typical of the duodenal ulcer type. An operation for duodenal ulcer was done two and one-half years before consultation. There were constantly recurring symptoms of gastric disturbances.

The following is a brief sketch of the psychologic aspects of the case:

The patient was second in a fraternity of five children and was the only son. As will be seen from the schematic outline of the family history, the parental influence was of a negative character. The patient was highly emotional. He was inclined to be distractable in conversation and approached the point at issue in a circuitous manner. His experience memory was poor. He learned easily, but did not retain factual knowledge. He displayed a marked feeling of insecurity, and this expressed itself strongly in his vocational adjustment. As a research engineer he had had several marked successes. He stated, however, that his conclusions were reached largely by intuition, and that he could recount with difficulty the logical steps by which he must convince his co-workers. Consequently he preferred to work alone, because it gave him a greater sense of security. He offered his stomach trouble as the reason why he held a mediocre position. It enabled him to work under conditions which offered the least possible emotional and physical strain. The patient was meticulous in his dress and was finicky about food. The latter he said was so because of his indigestion; still he admitted that the discomfort continued despite the dietary precautions.

He was married at 33 years of age to a woman three years his senior. She had been his father's favorite music student and had so far identified herself with the family before she met the patient that she called him "father." The patient's only child, a daughter, was born eighteen months after marriage. She lived only two and one-half years, and died two months previous to the patient's first visit to the clinic. The marital relationship was greatly conditioned by the wife's religious views, but he insisted that total abstinence did not affect him adversely. "My stomach is bad and that takes a lot out of a fellow." (Or were his stomach symptoms a compensatory adjustment for this lack of virile expression?)

During the first few interviews the patient talked freely of himself, yet one gained the impression that there was something that greatly troubled him which he was unwilling to disclose. Finally one morning he told the following story:

At 18 years of age he had his first and only premarital experience with a woman. At this time he was infected with gonorrhea, but he did not report for treatment until the disease was far advanced. With proper therapy, however, all symptoms were relieved. Several years later he went to a competent physician, who, after repeated tests, was unable to find any gonococci. A subsequent examination, likewise negative, was made just previous to marriage. Yet in the patient's mind there always remained a doubt and a terrific feeling of guilt.

When he realized that his wife was to have a child, his fears increased and caused him to omit intercourse. During the period of pregnancy, his first gastric symptoms developed, and they grew increasingly worse as the pregnancy progressed. The final blow fell on him when the child was born a mongolian idiot.

13a. In the case reports, P.O. indicates after operation, and N.O., that an operation had not been performed.

To the patient this tragedy confirmed his secret fears, and he held himself directly responsible. The child's malformation became the constant evidence of his guilt. So great were his fear and humiliation that he never mentioned the infection to the physicians who took care of the child.

The patient was operated on for ulcer three months after the child's birth. While giving this point in the history, he asked: "How could that operation help me when I had that child always before me?" He was unwilling to have another child. Consequently, because of her religious scruples, the wife refused intercourse. There still lurked in his mind the fear of infecting her, and he rationalized her resistance as only another penalty that he must pay for his guilt. At this interview the lack of any relationship between the condition of the child and his gonorrhea was carefully explained. The patient understood it and for the first time accepted it.

Ten days after the foregoing history was divulged the patient was anxious to review the effect of his confession. He said that the term "deliciously refreshed" most aptly described his new attitude toward life, and he reported that he and his wife had decided to have another child. The patient said that he thought this new and free relationship with his wife was also an important factor in changing his attitude, and in eliminating the sense of guilt that had previously inhibited his sexual life.

A week later the patient reported that he intended to move into a new apartment in order to get away from the constant reminders of the mongoloid child. His wife revived her interest in the further study of music. As a result of these changes, the patient found that he now could talk to his wife with the conviction of a man. There had been no gastric symptoms since the interview in which the gonorrhea episode was revealed, though the wife's studies necessitated his having the main meal away from home. This he had always carefully avoided in the past. Furthermore, he found that he had a different attitude toward his work, which was evidenced by the fact that boys in the office had been asking him lately what his good news was.

Further and more detailed analytic treatment with this patient does not seem necessary at the present time. He shows remarkably keen insight into his present condition and is intelligently making adjustments. Once the insufferable load of guilt was taken from his shoulders, his entire attitude toward life was altered.

Analysis of the Family History.—The paternal grandfather was a chronic inebriate, and the responsibility for the care of the family was left to the grandmother, who displayed ability and domineering qualities of personality. This reverse in the home situation had probably conditioned the lives of the patient's father and his sibs. A sister and two brothers were never married. Of these three, two showed strong maternal attachments. The patient's father married at 18, adapted poorly, and at 50 gave up a brilliant musical career and returned to the childhood home and the business of the mother.

The patient's mother was unstable emotionally and at times was unable to cope with life's problems and retreated to drinking. Little is known of the members of her family.

The patient was an only son, and there were four daughters. Neither of the parents had a positive influence in the home, or in the life of this sensitive boy. None of the sisters had adapted well to marriage.

All the members of this family except the mother were of the long thin variety. The youngest sister of the patient showed the only other evidence of gastrointestinal weakness. Two cases of tuberculosis were found in the paternal line.

Schematic Pattern of Patient's Family History

CASE 2.—*Racial Extraction:* Irish.

I.

F. Father	*F. Mother*
Died at 60 years. Delirium tremens. Chronic alcoholism.	Died at 80 years. Capable, domineering woman, maintained the position as head of the family. Managed business successfully.
Owned small country store. Unsuccessful. Wife managed business and family.	

II.

F. Brother	*F. Brother*	*F. Brother*	*F. Sister*	*Pt's Father*	*Pt's Mother*	*Two Brothers, One Sister*	*M. Brother*	*M. Sister*
Lived to 60 years. Athletic build. Health good.	Lived to 50's. Athletic build. Health good.	Died in early 30's of tuberculosis of the hip. Medium build.	Died in early 30's of tuberculosis of the lungs. Short, slender.	Living, 57 years. Medium height; slender; sharp, finely chiseled features. Health good.	Living, 56 years. Short, stout. Delirium tremens in 30's. Excessive drinking from 30-48 years.	Died at 40-50 years of age. No further information.	Farmer in Michigan. Not married.	Quiet, retiring. Married; several children. No further information.
Wealthy successful merchant in Dublin. Domineering personality. Hobbies: fishing and hunting. Married. Two children.	Accountant; moderately successful. Fisher and hunter. Never married. Lives alone in regal bachelor style.	Managed country store of mother. Not married.	"Lived for and with mother." Fear of going out alone. Few social contacts. No men friends.	Voice teacher with high standing. Poor financial provider. Completely absorbed by work, 8 a. m. – 10 p. m. Gave up teaching 7 years ago. Temperamental maladjustment. Now runs small country store. Wife's condition precipitated change. Violent temper. Married at 18 years. Little interest in family.	Woman of marked social charm and grace. Maladjustment in home led to drinking. Has begun several business ventures; interior decorating. Personal habits cause failure. Excellent music and art critic. "Peculiarly sweet and tender person." Married at 17 years. No drinking after birth of last child.			

III.

Sister	*Patient*	*Sister*	*Sister*	*Sister*
Medium height; slender. Health good.	Medium height; slender. Acute rheumatic fever at 15 years. Duodenal ulcer.	Medium height; slender. Club-feet—operative treatment. Health good.	Short; slender. Long history of chronic eczema during childhood.	Medium height; slender. Chronic constipation. Indigestion—care in selection of food controls this. Living, 23 years.
Took mother's place in the family. Domineering, critical. Married at 20 years to physician. Adaptation poor. Extravagant, selfish. Two children. Little attention to or apparent interest in children.	See case 2.	Quick tempered, erratic, indecisive. Only member of family who defied father during his temper tantrums. Came to America at 30. Married shortly afterward to ship acquaintance. First male friendship, unhappy marriage—history of frequent separation with impending divorce. Three children.	Quiet, gentle, sensitive. Usually cried during family quarrels. Married at 23 to a physician. Three children. Constant friction. Money distribution and his attention to other women. Divorced. She now manages a hotel and is a successful executive.	Critical, argumentative, self-assertive. Has set ideas. Selfish determination to lead her own life. Ambitious. Holds good secretarial position. Maintains her own apartment. Many men friends though she scoffs at marriage in view of the maladjustment of her parents and sisters.

CASE 3.—*Gastric Ulcer (P.O.)*.—In order to save space, the routine hospital history of the gastric disturbance will be omitted. The patient, R. L., had a classic case of peptic ulcer of the lesser curvature and received both medical and surgical treatment. Not only did his stomach symptoms recur, but other evidences of vegetative nervous system maladjustment developed; for example, sweating, trembling and fatigue. The following notes are presented in order to display something of the patient's "man-environment unit."

Morphologically, the patient showed that in thirty characters and indexes, 73 per cent fell well within the values that have been established for the ulcer group. It is interesting to note that the gonial angle, which has been found to be one of the most constantly specific characters in different constitutional types, in this instance was 106 degrees, a figure far more typical of the gallbladder race than of the ulcer race.

On April 26, 1926, a partial gastrectomy with entero-enterostomy and gastrojejunostomy was performed. The patient made a good recovery and was discharged on March 30.

On March 3, 1927, the patient was in good condition as far as the gastrointestinal tract was concerned. He was a bit underweight. He belched gas slightly.

On March 8, 1928, he continued in good shape, and was working regularly.

On October 19, there was no recurrence of the gastric symptoms, but the patient was troubled with profuse sweating. He presented another example of anxiety as a factor in the production of ulcer.

At this point the patient was turned over to the Constitution Clinic.

On Oct. 31, 1928, the patient presented a remarkable instance of the effects of chronic fear. His emotional maladjustment began at an early age with the experience of watching his terrific mother knocking out his drunken father and seeing the latter crawl ignominiously off to bed. But his mother never hit him, and he always felt happy and secure in her presence. After her death he was practically thrown out of his home by an older sister who took charge. A year or so later, at 16, he married, and he became a father at 18. After the third child he could not meet expenses and suffered the humiliation of breaking up his new home and seeing his wife go back to her mother. Subsequently he got it established again. Then came a revival of father troubles, ending in the forcible eviction of the drunken man from his house. Later his wife metaphorically beat him (the patient) over differences of opinion. After one of these altercations, he crawled off to bed with a sense of defeat, saying: "I never win." Yet in nightmares he was in dire difficulties and always waked calling his wife for help. Eleven years before examination he ran over and killed a child with his motor truck. He was acquitted; however, for years he was irritable at home. Further trouble developed with his father, and he was irritated at having the court order him to contribute to this parent's support. A conflict appeared. If he gave up driving the truck, he faced the loss of his home. But driving a truck revived the fears associated with the killing of the child. The patient then began to get insight. As a result, the sweats stopped; sleep became sound and normal; appetite returned; weight increased 2¼ pounds (1 Kg.) in ten days, and altogether he felt like a new man.

On November 7, the patient said that he had been eating better lunches without symptoms. He had no more sweats. He was less irritable with children. He noticed that he worried less. He was trying the device of asking his children for advice in small matters, and it worked well. He complained of headaches. The top of the head was flushed.

On December 12, the patient continued to do well. There was an interesting relapse of sweating following a motor accident on a hillside the week before. The patient saw its import and felt very well the week of examination. He had gained a little more weight.

On Jan. 11, 1929, the patient had gained 2 pounds more (0.9 Kg.)—he now weighed 137 pounds (62.1 Kg.)—a total gain of 5½ pounds (2.5 Kg.) since Oct. 31, 1928. He had had no more sweats. He felt fine; he did not have gastric symptoms and he ate practically everything.

On March 21, 1929, the patient had no complaints; he was free from sweats; his nervousness was limited to driving a truck in very slippery weather. He weighed 139 pounds (63 Kg.).

On April 19, the patient showed a marked improvement since starting work in the Constitution Clinic on Oct. 19, 1928. He had indulged, however, in food that seemed to be putting unnecessary stress on his stomach. Occasionally, he ate corned beef and cabbage and other indigestible foods. He was advised to follow a bland nourishing diet without restrictions except such vegetables and fruits as were apt to be tasted after eating or repeating vegetables. The patient was advised to return to the Constitution Clinic.

On Oct. 18, 1929, the patient had no pain or distress after meals. He was not on any diet. He was driving a truck as usual without dread.

On November 15, he said that five days previously, following a choking spell on drinking water, he vomited a teacupful of bright red blood. This stopped spontaneously, and he had had no recurrence.

The patient had a friend—an assistant timekeeper in the same firm in which he worked—with whom he used to compare symptoms. The friend's symptoms were attributed to gas in the stomach pressing on the heart. On Monday, November 4, the patient heard that this friend had died two days before while reaching for the paper at home. From October 21 to 29, the patient had been off work because of a cold. Worry over the friend and his own past symptoms made work more nerve-racking for the patient, and this led to fear of consequences of leaving the job again.

Hemorrhage occurred on Sunday morning, November 10. (This six day interval is characteristic of what we have found—usually a hemorrhage seems to occur from two to six days after the inciting cause.)

The patient talked to me for nearly two hours. He said that all the trouble started two years after his father came to stay with him in 1923. (Fifteen years previously his father lived with a married daughter; she promptly got stomach symptoms and paid $50 a week to doctors as long as the father lived with her. When he left, all her symptoms disappeared.) The patient unconsciously used interesting expressions in speaking of his father. "He used to turn my stomach"; then, referring to the money ($2.50 a week) he contributed to his father's support, he said, "Why should I bleed myself to death for him after the deal he gave me as a child?"

The patient's dreams of death may have come from the repeated remarks made by the father: "Don't talk to me about drinking—you'll be dead before me."

On Oct. 10, 1930, there were no symptoms referable to the patient's digestion, except occasional belching of gas when he ate too big a meal. He had recently had a fractured left arm which had laid him up and prevented him from working.

Summary.—The father's alcoholism and the accident of killing the child with a truck were, of course, serious blows. However, in view of the fact that the patient had seen the power of his mother over his father and his own experience with his wife's power over him, his failure to hold his home together was even

Schematic Pattern of Patient's Family History

CASE 3.—*Racial Extraction:* Irish. Both parents born in Southern Ireland.

I.

F. Father	*F. Mother*
Died young, accident.	Died shortly after husband's death — apparently from grief.

II.

Patient's Father	*Patient's Mother*	*M. Brother*	*M. Sister*	*M. Brother*	*M. Sister*
Medium height; slender. Living, 65 years. Chronic alcoholism. Health appears good.	Medium height; stout. Died at 50 years of "dropsy." Energetic, fast worker with little patience with attempts of others. Felt that she could do things best. Good manager. Full charge of home and finances. Usually happy and cheerful. Meticulous care of children and home. Superstitious. Instilled fear into the children.	Medium build. Living, 68 years. Chronic alcoholism.	Living, 74 years. Health good.	Died young, of pneumonia.	No information.
An only child who was early forced to "shift for himself." Stubborn, self-assertive, demanding, selfish. Was subservient to wife while she lived. Now determined to have his own life at the expense of his children.		Quick tempered, sensitive, suspicious. Self-assertive. Argues over the merest detail. Ferry boat fireman. Married. Two children.	Obstinate, self-assertive, independent, self-sufficient. Refused support from children at death of husband. Maintained herself by housework.		

III.

Sister	*Brother*	*Brother*	*Patient*	*Sister*
Five feet, 5 inches; stout. History of mild digestive disturbances. Living, 45 years	Tall; slender. On the road in vaudeville for 20 years. No contact with the family. Married. Divorced.	Five feet, 5 inches; slender. Chronic alcoholism for 10 years. Gave up drinking completely 5 years ago.	Five feet, 6 inches; slender. Headaches with excitement. Great fear of illness and a tendency to simulate symptoms. Gastric ulcer.	Died at 16 years. Rheumatic heart disease. Menses 15½ years.
Slow, steady, even tempered person. Happy, good natured. Self-confident. Little interested in the opinion of society. Considerate. Married. One child.		Quick energetic worker. Appears never to tire. Hustler. Electrician, foreman. Often takes night work in addition to regular job. Sings, dances, gives readings. Good entertainer. Enjoys the limelight. Happy, good natured. Appears to be untroubled by his environment. Married 21 years. Six children.	Case 3.	

more destructive. He had attempted at a very early age to demonstrate that he was a man, but he had failed to achieve the standards of manliness which he had set for himself. Furthermore, he was very precise and fussy over details about the house. In telling every one his faults, he displayed a masochistic tendency. He thought that people tried to humiliate him by showing that they were more capable of financial success than he was.

Analysis of Family History.—The patient's father was alcoholic and domineering, and he continued to be a destructive influence in the patient's life. The mother and her sisters showed definite virile trends. The mother was a combination of calmness and good nature and an urge to manage and carry on alone without cooperation. A maternal uncle evidently had an ulcer psyche pattern.

Two of the patient's brothers showed artistic leanings and were driving, restless spirits. The living sister was the opposite, a quiet, calm housewife with marked maternal interests. The youngest sister of the patient had rheumatic heart disease and died at 16 years of age with the onset of the menses.

In general, this family represents the tall, thin type, though the mother and sister are short and thick set. Several instances of evident gastro-intestinal weakness appear.

CASE 4.—*Duodenal Ulcer (N.O.).*—The patient, F. L., was a woman of 35 years who looked about 25. She was of a tall, slender build, and except for the gonial angle of 118 degrees was a classic example of the ulcer race. At 78 her father was a healthy man, though at 40 he had a nervous breakdown. Her mother was 78 and a very vigorous dominating person. The patient had two sisters, one older and one younger than herself. The oldest was injured in childhood and had been mentally and physically retarded ever since. The patient grew at the average rate, but her menstruation did not begin until she was 18 years and 10 months old. Up to that time she had been involved in what she described at first as a childhood and then a platonic boy and girl friendship, apparently utterly unaware of the significance of a possible love emotion. When she one day suddenly realized that the nature of the relationship had changed, she began to feel ill, and a few days later she had her first gastric hemorrhage. She was 19 years old at the time, and soon afterward she became engaged to this friend and marriage was much talked of for two and a half years. The engagement was broken, however, by the fiancé, who felt that he could not face the responsibility of a sick wife. The patient herself recognized that the prolonged gastric invalidism, which required great care and treatment for the whole of the following year, was a protection against further advance into a love relationship and marriage. Yet when her sister informed her that her former fiancé was again engaged to be married, she became most indignant. When she was 23 years old, she had an attack of mumps with ovarian involvement. The patient became engaged again when she was 25, but there was great vacillation about the marriage, which was arranged for and postponed many times. During this period she became involved with another man, and had an incomplete intercourse which resulted in pregnancy. This was interrupted at the second month, and for the following year the patient was in a very poor state of general health with much gastric disturbance. Subsequently she resumed sex relations with her fiancé, although never satisfactorily, and this state of affairs went on for the next two or three years. The question of marriage was continually discussed and postponed.

Two years before examination her fiancé told her that he had ceased to love her and had given up the plan of spending the summer with her. Twenty-four hours after he delivered this ultimatum, she had a severe gastric hemorrhage. Her recovery from this attack was slow. She presented herself at the clinic with the

history that she was constantly fatigued, could eat almost nothing without subsequent distress and was often moved to tears at the slightest emotion. About three months before admission she had received a cable from her fiancé saying that he was not coming to Europe as planned to join her. Within twelve hours, she suffered from a return of gastric distress with vomiting.

As the patient told her story, she made continual references to her need of some dependable human relationship. "I must have one person whom I can trust completely." Yet she perceived that all the men she had turned to had been quite vacillating and undependable. "Indeed," she declared, "every man I've been in love with has developed some reason why at the last moment the relationship had to be broken." She found them all "unlike my wonderful father who is the only man I've ever known who embodies all the virtues, and particularly the great essential quality of loyalty."

The suggestion was then made to her that perhaps her own attitude toward the opposite sex had an antagonistic element in it which led her to select men essentially unsuitable for permanent mates, or that perhaps she had an unconscious resistance to marriage itself. Such possibilities were consciously denied, but within a few days she dreamed that she attended an entertainment. At the door a boy said to her "come in here and see the show we men are going to give." The immediate association took her back to events that had occurred when she was 5, which she had not thought of for many years. At that time she had been living with her aunt because of her father's illness, and she recalled the terror she had experienced every day on going out into the garden. There she was tormented and frightened by a small boy who chased her and pulled her hair. For several interviews these apparently harmless gestures were recounted as the only ones. But finally, with tears and averted gaze, displaying emotional disturbance and embarrassment out of all proportion, she stated that the little boy had likewise made her acutely ill with nausea and vomiting by the exposure of his genital organs.

The patient soon began to realize that all her emotional reactions were of an extremely childish sort. She confessed to a strong desire to consort with her younger sister's friends, and she noted herself the swift change from tears to laughter which so characterized her. She had gained insight into the mechanism of her retarded psychosexual development represented by her late menstrual onset, the avoidance of marriage, the incomplete sexual relations and the idealization of the father. On the thinking or rational side, she had attempted a compensatory effort at independence and self-sufficiency. With the growth of insight, there had been a definite gain in vigor and the ability to eat any kind of food without distress.

Analysis of Family History.—Longevity appeared in the maternal line. The mother and all of her sisters seemed to be of a vigorous and striking personality with tremendous driving force. There was a distinctly low interest in marriage associated with strong church affiliations. The mother of the patient exhibited a marked inferiority complex with a nervous drive to overcome this. One brother had been married three times.

There was a strong trend of nervous instability in the father characterized by complete collapse in the face of difficulties. He displayed terrific driving force in his work.

Neither the patient nor her two sisters were married. The oldest suffered from a mental breakdown following a spinal injury at 19 years. At 38 years she showed rather good recovery through suggestive treatment. The youngest sister was 28 years of age. She was a rather timid, retiring, introspective girl, with a sense of insecurity covered by an attitude of blasé boredom.

Schematic Pattern of Patient's Family History

CASE 4.—*Racial Extraction:* Old American, English extraction.

I.

M. Father

Tall, well built, vigorous man. Died at 86 years. Premature gray hair.

Mechanic—successful. Active in business until 80 years of age.

M. Mother

No information. All members of her family died in the same accident.

II.

F. Sister

No information.

Father

Five feet, 10 inches; thin, wiry. Living, 75 years. Health good.

Tender, sympathetic, tolerant. Highly suggestible. Abnormal fear of death. Man of terrific energy and nervous activity. Several periods of depressive psychosis 40-50 years of age. Always subject to marked depressions due to a sympathetic response to another's troubles. Successful engineer. Married at 35 years.

Mother

Five feet, 5 inches; 165 pounds. Living, 78 years. "Remarkable physique." Premature gray hair.

Self-conscious, timid, nervous, easily excitable. Social functions followed by complete physical exhaustion. Constantly nagging over details in the family, genial and courteous to strangers. Dependable in emergencies, collapses when strain is past. Married at 37 years.

M. Sister

Five feet, 6 inches; slender. Living, 86 years. Active, healthy. Premature gray hair.

Severe Puritanical type. Irritable, fussy. Worries herself and all around her regarding details. Enthusiastic church worker. At present does all of her shopping and never seems to tire. Not married.

M. Sister

Medium height; slender. Living, 83 years. Health excellent. Premature gray hair.

Much like spinster sister in temperament. They live together and share the same interests. Married young, husband died shortly after marriage. No further interest in marriage.

M. Sister

Died young, childbirth. No further information.

M. Sister

Short, medium. Living, 60 years. Health good.

Dictatorial, domineering. "Rules the roost and husband." Unbending Puritan. No children.

M. Brother

Six feet, 2 inches; well built. Living, 62 years. Health good.

Successful merchant in father's business. Married. No children.

M. Brother

Five feet, 9 inches; medium. Living, 52 years. Health good. Premature gray hair.

Actively identified with liberal politics since 30 years of age. Independent in action. Broke from Puritan traditions of the family. Genial, well liked, carefree person. Nervous habit of twitching hand. Otherwise, always calm and well poised. Married three times. Wives were all active forceful women.

Sister

Five feet, 7 inches; medium build. Accident to spine at 19 years. Slow physical recovery followed by mental disturbances. Fair recovery at present. Living, 38 years.

Introspective, silent, deep interest in religion. Self-conscious, hesitant in speech. Powers of observation keen. Tense nervous contraction of muscles. Whole personality probably conditioned by after-effects of accident.

Patient

Five feet, 7 inches; 120 pounds. Living, 35 years. Duodenal ulcer. See case 4.

Miscarriages

Two or three in succession. One known to be a male.

Sister

Five feet, 7 inches; 120 pounds. Health good. Living, 28 years.

Outwardly complacent, calm, undisturbed by environment, self-sufficient. "Lives within herself, no one ever knows what she is thinking or planning." Really somewhat timidly retiring and socially insecure. Closest friends are women. Little interest in marriage.

The members of this family were of the tall thin variety. There was no evidence of a constitutional inferiority of the gastro-intestinal tract in the family.

The following histories are presented in somewhat different form from those which have just preceded. The object of this difference is to indicate the possibility of the nonanalytic approach to the psychologic panel.

Case 5 (64097).—*Duodenal Ulcer (P.O.).—Family History.*—Paternal: The history of the father's father was not known. The father's mother died at 80. She possibly had a carcinoma of the breast (jaundice and ascites). Her height was 5 feet, 5 inches, and she weighed 200 pounds (90.7 Kg.). She was broad faced, mild tempered, easy going, and not worrisome. The father's brother ran a ranch in the West. He was the "damnedest liar in forty-eight states." The father died of pneumonia at 60. He had a hernia for many years. He was 5 feet, 7 inches tall; he was fat in his youth, but later lost weight. He had round features. He was fairly clean in his habits. He was deliberate.

Maternal: The history of the mother's father was not known. The mother's mother died at 72, of some heart disease. She was small, small-boned, and heavy as a young woman. She was very religious, fanatical, exacting, and bigoted. The mother died at 59, of heart trouble and asthma. She was a little woman with small features, and was fleshy; she had eleven children. She was troubled with gas on the stomach. She was energetic, nervous, and frightened easily by little things, though not by important ones. She was careless with money, sensitive, quick-tempered and a good housekeeper.

Siblings: 1. A brother, aged 54, was of medium height, and stocky; his health was good. He had married at 19 years. He was even and deliberate in manner. He had a jovial nature.

2. A sister was of medium height and stout. She had hypertension, nephrosis and obesity. She was impulsive, suspicious and suggestible. She was a meticulous housekeeper.

3. A sister was short and stout. She had severe headaches. Her marital adjustment was poor; she was divorced, and then remarried. She was a good mixer and entertained well. She was sensitive, quick to cry and sought sympathy. She needed public confidence.

4. A brother was of medium build. He married at 21 years; he remarried after a divorce. He was a heavy drinker at times. He was a quiet, retiring person, and was dependable. He was careful of his personal possessions and was aroused when these were disturbed.

5. A brother was of medium build. He had pneumonia and slight rheumatic pains. He was the most stable member of the family. He was jovial and happy-go-lucky, and was not a fighter.

6. A sister died at 42 years of congenital epilepsy. She had an epileptic constitution.

7. A sister, 5 feet, 1 inch tall, was very stout. She was a jovial, sociable person who liked to be out with the crowd. She was generous, kind and even-tempered.

8. A sister had epilepsy. Her condition was said to have developed at 14 years of age, when she had an operation for an abscess at the base of the skull. She was institutionalized. She was married and had one normal child.

9. This sibling was the patient, S. F.

10. A brother died in infancy of cardiac failure.

11. A brother was of medium build. He had red hair. He was a taxi driver; he changed jobs often. He displayed a quick, intermittent activity. He married at 18 years, was divorced and remarried. He was markedly gregarious. He was suspicious of personal insults.

12. A brother was of medium build. He had been gassed during the World War. "Neither his health nor his mind have been good since." He had attacks of sharp pain in the abdomen. He was married and divorced twice.

Personal History.—The birth and early development were normal as far as is known. The patient remembered being taken from his home by a friend as a joke at the age of 7 (the family thought he was kidnapped). His childhood was happy. He had many friends and playmates. He left school at 14, when he was in the eighth grade, and went to work in a laundry. He had several jobs, each lasting a few weeks, till he was 17, when he started to learn draughting. He stayed at this work for about two years (?), and he said that he should have stayed longer because he had a goal, but he fell out with his boss and left. He had other odd jobs. For the past eleven years he had been a chauffeur, both private and taxi. He married at 25, but the adjustment was bad. He married above his station (wife was a concert singer); he was unfaithful and contracted gonorrhea at 27. He was divorced about five years before consultation. He married again six months before this admission. His wife was below (?) his station and fifteen years younger than he was. She had a rheumatic heart condition, which interfered with child bearing.

Personality.—Intellectual Activities: The patient went to the eighth grade in school but did not graduate. His drawing and penmanship were especially good; his history and grammar were good, and his mathematics and geography were poor. He learned some things easily, but his concentration was poor and if he did not get the hang of things he lost interest and "side-tracked it." His visual memory was excellent; his experience memory was good, and his auditory memory was poor.

He was very handy with tools; he doubted his ability to manage others well, and had never tried it.

He had little common sense. He was never able to save money, and was extravagant. He laid plans deeply, but did not really plan well. People did not seek his advice. He was very distractable. He was quite definitely dreamy; he felt above his environment and tried to rise above it. He said: "Would like to be better off than I am."

He was probably introverted, and he believed that he would get better off "by luck."

He was not very scrupulous of the rights of others.

Somatic Demands: The patient was fussy about food; he said that he was hard to suit. He ate well and often, but said that he did not overeat. He ate spicy foods; he drank ten cups of coffee a day, and smoked thirty cigarettes daily. He was very fond of attention, and rather vain. He was fond of luxury and comfort.

He was active, but by fits and starts. He arose early every day, and worked hard for a short time and then rested. He was enthusiastic for short periods.

He was definitely attracted toward the opposite sex. He had rather strong sexual desires and placed little restraint on himself.

His friends were apt to be more intelligent than he was.

He had no family attachment. He married twice; neither marriage was successful.

Self-Estimate: The patient did not usually feel ill at ease or timid, though as a child he was. He was rather negatively suggestible, stubborn and conceited. He sought company, though he did not become lonesome easily. He was confident of himself as a driver. He was very frank and open. He liked to be the center of attraction, and was rather vain. He was generous to a fault. He was not guided by principle, but grasped opportunities. He drove very well in traffic. He changed jobs frequently. He was always "looking for a stroke of luck." He accepted new plans quickly.

Mood and Emotional Reaction: The patient was usually cheerful and optimistic. His mood was variable. He said that he was "quick on the trigger," but was over his temper quickly. Painful stimuli gave a marked reaction. He was neurotic and complained under pain and discomfort. He was rather easy to frighten. He cited instances in which fright caused "dripping perspiration." He said that as a child he was "cowed" by his fellows. He was easily elated by pleasure. He did not worry or harbor grudges long; he forgave easily. He said: "Kind words take the fight out of me."

Adaptation Imperative: The patient was not really ambitious; he was not very courageous, and he had little real initiative. He was somewhat vigorous minded. He said: "Opposition stirs me on." He had liked active sports as a boy. Carpentry was his hobby. He liked the theater. He enjoyed a few games. He was still interested in penmanship and wrote a very pretty hand. He read books on psychology and was interested in "self-analysis." He said that he "tries to find out hidden meanings." He used little restraint in the appetites, fears or passions displayed.

Evidently this patient is fussy over details of food and dress, is vain and fond of attention and has not been successful in his two marriages. He was shy in childhood, easily frightened and cowed by his fellows. His statement that "kind words take the fight out of me" bespeaks of an emotional sentimentalism, not of distinctly masculine character. Yet it should be noted that his heterosexual urge and activity are unusually strong.

Case 6 (65118).—*Duodenal Ulcer (P.O.).—Family History.*—Paternal: The father was of English stock (Bermuda). The father's father was a ship builder. He was a "neurotic in the end." The father died of stomach trouble at 65 years of age. He was a tradesman and cooper. He was of medium size, thin and nervous. He was a great smoker. He married a second time when the patient, N. B., was 25. One of the father's brothers was slightly weak-minded "due to drink," and died at 40 years of alcoholism. Another of the father's brothers died of smallpox (no age given). Still another brother died at 68 years of stone in the kidney.

Maternal: The mother was of Scotch stock. The mother's father was a sea captain; he taught navigation in Bermuda. She was a fine type. The mother's mother died of heart disease at 64 years. She was rather small, very thin and active; she was always in a hurry, ran and never walked. She usually seemed tired.

Siblings: There were five sisters; two were dead. One "went off her head" and tried to commit suicide. Spinal difficulty and "efforts of a doctor to cure this, resulted in loss of mind." The oldest sister was 74 years of age. One brother was 72 years of age and worked regularly as a stone mason. He had seven children

by his first wife and four by his second. Another brother was alive and well at 57 years. One sister was a neurotic; she had dysfunction of the liver.

Personal History.—The patient had a fairly happy childhood. He had to do many chores; yet, he had time for things of other sorts. His father was a good companion. The patient was not considered a healthy child; he had many colds, mumps, chickenpox, measles and scarlet fever. He was ill during the latter part of his life. He had scarlet fever when he was 40 years old. An operation had been performed on the kidneys some years before examination, either for infection or for stone.

The patient went to school at 10 years of age and did fairly well. However, he left school at 14 years so as to be made "useful." He was sent to learn the trade of harness making. His father always directed his course and never allowed him to do what he wanted; invariably he was told what to do.

The symptoms of the present illness dated back a long time. The first serious symptoms appeared in 1912, when the patient was a steward of a country club in Flushing, N. Y. His position was congenial, but there was a good deal of drunkenness among the members. He had to handle them with care; this was a strain; also, there was night work with irregular hours. However, the patient could think of no sharply precipitating cause of the present condition.

Personality.—Intellectual Activities: The patient learned easily. He was good in spelling; he liked geography. He was not good in mathematics. He had always tried to please in his positions, but he had a roving disposition and liked to change.

His retention for recent events was rather poor; he remembered remote experiences more easily than recent experiences. His visual memory was good. His power of concentration had always been bad, chiefly because he "sees too many things at once." The patient said that he was overtimid and lacked initiative; he was not bold enough. He spent money very unwisely; if it had not been for his wife, he would not have had any.

He was very good with his hands, but not dextrous.

The patient had handled small groups of men (thirty) successfully. He has a good respect for the rights of others. He was imaginative.

His dreams were generally very horrible. One night he dreamed he had poisoned his father. His head was separate from the body. He placed it on the table and asked it to forgive him. There was no answer, but the eyes opened and shut. He awoke in horror. On going to sleep again, the head was still there; it asked him to stoop down. The patient then felt the cold lips on his ear. He awoke in horror. This dream stayed with him for weeks. Again he dreamed that he had crawled through a tunnel in a sand pit, and was almost suffocated. Also many black cats scratched him. He felt blood from the scratches. A friend, an older man, said that he would help him out; then another black cat scratched him. The dreams were always frightening and distressing. Since he had been in the hospital, the dreams had always been of bodily discomfort. He did not walk in his sleep.

The patient was truthful. He was not introspective. He liked nature and studied people. He left himself out of the picture, because he did not want to become nervous.

Before operation on the kidney he was very sorry for himself.

Somatic Demands: The patient did not use alcohol or tobacco. He had had the habit of biting his nails in childhood.

He liked attention, but did not seek it. He knew his capabilities and his limitations. He had a horror of the sight of blood. Once he saw a veterinarian open a horse, and this made him sick (10 years old).

As a child he was much frightened after dark; on coming up the cellar stairs, he ran lest someone catch his leg. He was very timid when learning to swim; he always imagined that a fish would bite him. He demanded activity. He tired easily and would often go home after playing games involving physical exertion, complaining of pain in his side; he was made to sit in a chair. He was not pugnacious, and was easily cowed by older boys. At school an older boy rather protected him. He was a continual worker.

In his sex-life, the patient was prudish and bashful. He practiced the average amount of masturbation. He had many girl companions. His sex experience was not excessive. His urge was naturally heterosexual. He avoided all suggestion of homosexuality. The patient had feministic trends. He sought friends among those from whom he could learn; his men friends were older.

The patient was especially (emphatic) attached to his mother. He married at 37. His mother died when he was 21 or 22 years old. He had been married twenty-one years and had no children. His wife was living.

He had a strong attachment to his brother and sister; they corresponded. He was always homesick until he married. His marriage was very successful.

Self-Estimate: The patient was not bashful or ill at ease in a crowd. A lack of schooling or training had held him back. He felt sort of "half-finished." He said: "Being a butler is not much to be proud of."

He was very trusting. He said: "I distrust no one till I find him out, and then that's the last of him."

He was handicapped with nerves. If there was a heated argument, he moved away. He said: "I wouldn't make a soldier." If he saw a brawl he turned away. He liked everything to go smoothly. The last few years he had struggled to accumulate enough to leave his wife comfortably off. This attempt had not been successful and had made him anxious. He was very loyal. While his feelings were easily wounded, he did not become angry or irritable. An injustice rankled within him. Anger always expended itself in his epigastric region (he pointed to it).

The patient was overreticent and very precise. His wife shook him out of this. He was tactful and not suspicious. People treated him well, he said, but he had few friends.

Mood and Emotional Reactions: The patient was generally cheerful; he was stable. He became unhappy quickly at times. He reacted buoyantly to pleasurable stimuli. His reaction to painful stimuli was slow, but it lasted long. The loss of a friend through death was hard. His fear of criticism was a tender point; he wanted to be well thought of. Physical fear was not a factor. Once, when the patient was almost run over by a motor, his only reaction was "how lucky it was on the right side and not on the left" (he had had a kidney operation on the left). He did not think that he reacted markedly to fear. He was inclined to brood.

Adaptation Imperative: The patient formerly had had ambitions to become an artist, a fine handworker or a jeweler, but his father forced him without discussion into the harness making trade. He left this work and took up tailoring for five years; he became a fairly good tailor. Then he went on a ship as steward and developed a roving disposition. Then he did club work and worked as a butler.

The patient thought that he was overcautious; he did not like to risk what he had. Initiative appeared only if in connection with something he knew about (caution again?). The patient was by all means a follower. His chief satisfaction was derived from his wife and home. He was not interested in sports. He liked reading and traveling. He was fond of music, especially sacred (there was much feminism in his intonations, expressions, etc.). He had always been a church

member, and was fairly religious. He attended church when at home. He did not enter into politics; he could not stand heated discussions. He showed a conscious restraint of anger, fear and appetites. He said that it was: "No job to control at all."

Special Traits: The patient thought that he could have been a painter or an artist. He occasionally did some painting in water-color, usually of flowers.

This patient was quite noticeably feministic in his general bearing. He frankly admits that he would not make a soldier. His mother attachment is indicated both by his murder dreams and by the fifteen year delay in marriage after her death. His feminism is suggested also by his occupation as butler. He should have been an artist but for his father, who overrode his ambitions.

The following excerpts from other histories also in some instances indicate the tendency to overexpress a masculine attitude. The emphasis is so great that one is led to suspect that the opposite influence is very strongly developed in the unconscious. In other cases, the histories display the patient's difficulty or inability to play a vigorous masculine rôle in life.

Gastric Ulcer Males.—The following cases are typical examples of the types mentioned.

Case 7.—For two years the patient was a cook. Later he took up the trade of bricklaying. He said of his driving activity: "I am the fastest bricklayer in New York." He boasted that as a boy he always won a fight. He felt that a refusal to accept help from his wife in any situation typified his independence of action. He said: "I have more self-control than any ten ordinary men," and yet the next sentence was: "I never let a habit get the best of me for once they are formed they get the upper hand." He boasted that no man could misuse him.

Case 8.—The patient had the habit of nail-biting up to 14 years of age. He was a letter carrier. He was active in the time of danger, but crumpled up when the emergency passed. He said: "I ate up my feelings when serving at the front and didn't digest them." His father had chronic alcoholism. The patient felt that his early home life was largely responsible for his emotional disturbances. His child's illness precipitated his ulcer attack. He was overly protective of his wife, and during this time he ate every meal for fear that she might suspect the gravity of the situation. (Here he found himself unable to play a wholly protective masculine rôle.)

Case 10.—The patient was the youngest of nine children. He boasted of his love affairs, but at 33 he was still looking for the "right red-headed girl." He said: "I could go to a dance every night in the week—yet I like to play cards and stay around with the fellows." He drank excessively.

Case 11.—The patient was a tailor. He had tried other occupations, such as chauffeur and automobile mechanic, but he always came back to tailoring. He married at 21 years. He showed extreme resentment of his stepmother and half-sibs. He particularly enjoyed describing the raw deal life had given him, and his disposition was of the feminine masochistic type. He was indecisive.

Case 12.—The patient had been self-supporting since 14 years of age. He left trade school to get a job. He planned his work well and was fairly successful as a contract painter. He married at 23 years. He said: "I was never able to leave

the ladies alone." Yet he was a regular joiner and was a member of thirteen men's lodges. He was an anxious, suspicious individual. He had materialistic standards. He said: "Have as much money as the other fellow and he won't look down on you." He was timid and bashful, and he said: "People try to make me look little." He traveled for prestige; he said: "It puts me above the other fellow." (He was evidently very unsure of his masculinity.)

Duodenal Ulcer Males.—The following cases are typical of the types mentioned.

Case 13.—A layman friend of this patient wrote a letter about him from which the following excerpt is taken:

"In my house J. was unstable, not responsible always, the same mixture of dreamer and drifter and keen pursuer of favorite ideas. His personal character was somewhat of the same mixture. He was unfailingly kind to the women in our group, even gentle in a sense usually understood as the characteristic of women rather than men. His sympathy would extend to the point of his own personal suffering. He was inarticulate usually, and upon his own difficulties very nearly silent. It was especially hard to watch his health because he resisted any attempt to do so and went around sometimes in silent agony because he could not bear to let anyone know he was so unmanly as to be sick."

Case 14.—This patient's symptoms began with the onset of the wife's first pregnancy. They increased throughout, and shortly after delivery, the ulcer perforated. He made a good recovery. Four years later, when the wife started her second pregnancy, he again began to have gastric symptoms. He stated that it upset him terribly to be responsible for his wife's discomfort; it made him nervous and caused him to feel like a brute. Indeed, he had the obsession of being almost the criminal cause of her condition and feared that she might die in childbirth. This patient was a classic type, small, slender and high-strung. His palpebral fissures were very wide, and he was always driving at his work. He managed the whole office, went out after new work and generally did the work of ten men.

Case 15.—This patient said: "I am not afraid of anything, why I'd dive into deep water before I could swim." He boasted of his heterosexual urge; "simply can't leave the women alone." Yet he married at 33 a woman older than himself, and he admitted on careful questioning that he was actually very timid with women. He was an old maid in respect to orderliness; he would leave the table to put something in place; otherwise, he would not digest his food. He said: "Painted face, dirty neck; well dressed men with shoes run down at the heel annoy me most." He was of the subservient servant type; he was a chauffeur and an apartment house superintendent. He changed his job often. He said that he "never had a row with the boss."

Case 16.—The patient was married at 20 years. He said: "I can do in one day what it will take another man two days to do." He was extremely sentimental and demonstrative. He fainted when frightened. He was weak and trembling when he had to confront his superior in his work. He was a Fifth Avenue bus conductor, and was markedly solicitous of the safety and comfort of his passengers.

In all of these histories and excerpts there is to be found a subtle and convincing evidence of the strong desire to overexpress virility. The same principles can be seen through the personalities of the female

patients. The following three complete studies of female patients are given as examples:

CASE 17 (36753).—*Duodenal Ulcer* (*P.O.*).

Family History.—Paternal: The father was of English stock. The history of the father's father and mother was not known. The father died at 56 of "lung trouble;" he also had dysentery.

Maternal: The history of the mother's father and mother was not known. The mother died of tuberculosis of the lungs.

Siblings: One brother died during the Civil War. Another brother died of tuberculosis, and still another brother died of "heart trouble." A sister died of tuberculosis of the lungs.

Personal History.—The patient, M. T., was very ill and was slow in her answers, but she seemed quite clear in the information she gave. She was born on a farm in the middle west, where she remembered a happy childhood. She was a tomboy. Her menstrual history started at 13. She was educated in private schools, and she traveled abroad several times. She started to write when a young girl, and she wrote words for Moody and Sankey hymns. The patient said that she had had "stomach trouble" since childhood. She married at 30. She never wanted children and caused abortions every time she was pregnant.

Personality.—Intellectual Activities: The patient learned easily in school, except in regard to mathematics. She disliked to study and was very distractible, almost flighty. Her power of concentration was excellent for short periods, but not for any length of time. Her memory was good in the visual field, but poor in the auditory field. Her experience memory was easily the best. On a previous admission, it was noted in the charts that she had a particularly bad memory for numbers and dates. She planned poorly; she said "it is too much bother." She had shown rather bad judgment all her life.

The patient was very clumsy with her hands; she disliked housework or anything manual. She was a good executive. She had been a dilettante at many things: writing, politics, women's rights, etc. She was not able to save money, but she said she had "stingy streaks," and was never without something.

The patient would not be called dreamy or visionary. She was very truthful and careful of the rights of others. She was definitely extroverted.

Somatic Demands: The patient was not particularly fond of her own comfort; she was not vain and was not very anxious for the affection of others. She had been a very hearty eater. She drank six or seven cups of coffee a day. She was always in a hurry; she worked hard all the while. She said that she "has crazes for things." She would be called pushing and aggressive. She was adapted poorly to marriage. She was a "tomboy" in her youth and early womanhood. She married at 30; sex relations were not pleasant. She had no desire for children and always induced abortions. She seemed to be a very well adjusted homosexual. She spoke of her husband as a "wonderful, simple little man." She said: "I have a good deal of masculinity."

Self-Estimate: The patient would seem to be quite self-confident and showed a feeling of insecurity only indirectly. She was rather negatively suggestible and stubborn. She was poor company for herself, and liked companions. She was frank and open in her attitude toward those whose opinions she respected. She was not vain, but "adored success." During a previous admission, she was delirious and expressed definite delusions, indirectly, perhaps, a fundamental suspiciousness (which might link up with homosexuality?). She was generous and not bound by principle, and she behaved definitely as an opportunist.

Adaptation Imperative: The patient was usually cheerful and optimistic, but said that she had rather marked and quickly succeeding swings of mood. She was quickly excited. She did not remember having ever been frightened, but she said that she would not have children because she was "afraid of the pain." She was not easily elated. Her moods were transient.

When the patient was ill or had pain, she became quite weak, though she claimed not to be affected. She said: "I hate to see women suffer."

She was ambitious and vigorous minded. She had a large number of outside recreative activities, but none was very engrossing. She always liked politics, and had gone to church occasionally. Lately she had become interested in Christian Science.

The patient had little tendency to repress her appetites or temper. She believed that she was brave, but really she was not. She said that she "has a hard time handling herself."

Again the "tomboy" appears. The patient disliked housework and the usual manual work of women, but enjoyed directing things. She said: "I have a good deal of masculinity in me." Her adjustments were not good, and there is some reason to believe that there was a strong homosexual trend.

CASE 18 (640066).—*Duodenal Ulcer (Confirmed by the X-Rays).*

Family History.—Paternal: The father's father and mother were German. The father had died at 72 of pneumonia. He had "acute bronchitis;" lumbago at 21, and "stomach trouble all his life." He was tall and thin and had angular features (he resembled the patient, J. P.). He was cranky, a scold, and fussy about food. He was not affectionate toward his children. He was artistic, and was very bitter against religion. He "thought churches materialistic."

Maternal: The mother's father and mother were German. The mother was also German. She died at 52, of cardiorenal disease (asthma and kidney trouble). She was short and plump. She was easy going, but was worrisome by spells. She was religious. She got along well with others. The mother's sister died at 70. She never married; she resembled the mother (she was short and plump). She was a governess.

Siblings: A brother died of "spinal meningitis" at 29. The trouble started with an earache; he was sick for one week. He resembled the mother in morphology and psychology. The history of the second child was not known. The third child, a sister, died at 15 months, of scarlet fever. Another sister had recently developed double vision and aches and pains. She was tall and wiry. She weighed 95 pounds (43.1 Kg.). The fifth child, a brother, died of "summer complaint." A sister died of acute appendicitis at 26. She was tall and angular, and resembled the patient.

Patient's Son: The son had had appendicitis. He was tall and angular. He was easy going; he was not married, and was quiet and agreeable.

Personal History.—The details of the patient's birth were not known. The history of her infancy was not known, except for scarlet fever. Her childhood was unhappy. The father was grouchy and not affectionate. The cervical lymph nodes had been enlarged and suppurating at 6 to 8 years of age, and required an operation, which left scars. The patient was sensitive about the deformity.

She was afraid of dark rooms and afraid to be alone; she would not undress until she had looked under the bed.

The patient liked active games and played with boys, but she did not believe that she was considered a tomboy.

She married at 19. Her married life was not particularly happy. A sexual adjustment was rather difficult. The patient said that her husband was "sporty," a gambler, and was unfaithful to her. He died when the patient was 27 years old.

The patient had tuberculosis of the lungs when she was 31 years old. She spent one year at Saranac and recovered. She was able to support herself and her son by her own efforts till the son obtained a position. He then supported her.

Personality.—Intellectual Activities: The patient was probably somewhat slow to learn. She left school at 16, when she was in the eighth grade (she was kept back somewhat by the tuberculous nodes?). Arithmetic and grammar were done poorly; history, geography and spelling were liked.

The patient believed that she was always rather distractible. She said that she "has many things going at the same time." She concentrated well for a short time. She was not very introspective and did not look into her own personal problems clearly.

Her memory was fair; it was better in the auditory than in the visual field. The patient had little sense of location and forgot her childhood German almost completely. She did not recognize faces very well. Her common sense judgment was fair, except in regard to money; she had not saved. She planned housework well, but not other things. She was rather quick in making decisions. She was fairly successful as an executive in a small way.

The patient was not considered visionary or dreamy, and she was not introspective. Her night dreams were unpleasant; they were of falling, sinking or being chased. She was truthful, but was not particularly careful in regard to the rights of others.

Somatic Demands: The patient's appetite was usually good, but as she had had stomach trouble since childhood, she had always had to be careful about overeating. She liked coffee, but it made her dizzy. As a child she had had vomiting spells and dizziness. She was always fond of comfort and fine clothes, but she believed that she did not care for affectionate displays.

The patient always kept busy and active. She said that as a child she always "tried to take everything in." She liked excitement, but was never able to stand it. She was sick after seeing Barnum's circus. She had rather frequent emotional discharges (temper tantrums) after which she would have a headache. She was not extremely aggressive, but would not be considered timid.

The patient's demand for sexual gratification was moderate, and her heterosexual adaptation in general was only fair. Still she was not particularly fond of her own sex, and would rather work for a man.

Self-Estimate: The patient was quite confident of her own abilities. She was not very suggestible. She was rather self-sufficient; she did not seek company, though she did not shun it. She was inclined to be somewhat reticent and evasive in a first contact, but seemed quite frank later. She was generous.

The patient was not unduly bound by principle or by a sense of loyalty. She left her employers without much cause and she had no religious or social duties that she considered very important. She was inclined to be stubborn.

Mood: The patient had no very distinct mood. She said that she was inclined to be pessimistic, but that she used to be optimistic. Her mood was fairly stable. She said that she was pouty and sulky as a child. She took a long time to get over real sadness, but stopped crying easily. She said that she never forgave a wrong. She was inclined to be worrisome and irritable. She is rather easily frightened and

got palpitation and chilly sensations while this occurred. She did not perspire. She had fainted from fright at times. She was rather impulsive.

Adaptation Imperative: The patient was not very ambitious, courageous or inclined to lead. She derived her deepest satisfaction from the love of her son. She liked theaters, dining out and music. She used to enjoy outings in the country, but had not been on one for eight years. She was not religious or interested in social work or politics. She read very light fiction (cheap love stories).

This woman, like the one in case 17, enjoyed games and playing with boys. She successfully supported herself after her husband's death. She preferred to work with men and was a successful executive. Her marital and sex adjustments were not good.

Case 19 (31557).—*Gastric Ulcer (Lesser Curvature, P.O.).*

Personal History.—The patient's birth and early development were probably normal. At 13 years she had rheumatic fever and was ill for fourteen weeks. She went to work at sewing when 13 or 14 years of age. She recalled that a man chased her for some immoral purpose when she was 13 or 14. She said: "I was so frightened I could'nt speak." She had little chance for social life between 18 and 25 years of age. Her gastric symptoms dated back about forty years, or to when she was about 20 years old.

The patient married at 35; she knew her husband ten years before she married him. Her married life was not particularly happy; she said she married twice. She had had no sex knowledge till the age of 14. Sexual adjustment was very difficult, and she had great difficulty with her labors.

Personality.—The patient was fairly quick to learn. She was good at mathematics and history, but disliked geography. She was inclined to be somewhat distractible in conversation, though she was very intense in her concentration. She was certainly not inclined to day dream or to be introspective. Her auditory memory was fair; her visual memory, poor, and experience memory, good.

The patient was matter of fact in her attitude toward the usual things of life, and her judgment was good. She, however, did not plan well, but took things as they came to her. She had never been able to save money. She was handy with tools and had been an excellent seamstress.

She was naturally a hearty eater, but had had gastric difficulty so long that she had become a careful eater and avoided meat and spices.

The patient was fond of attention. She was inclined always to be active, "on the go," probably overactive, enthusiastic and somewhat aggressive. It would seem that her sex differentiation was not complete. She never adapted well and declared that she would never marry if she had to do it over. She had been a good deal of a tomboy and loved outdoor games to the exclusion of dolls.

The patient was quick in her reactions. She showed embarrassment easily. Her reaction to painful stimuli was markedly rapid and exaggeratedly fearful. She was rather easily suggestible. She was gregarious, and became lonesome easily. She was inclined to be confidential and apparently was not very reticent. She was generous to a fault.

The patient would be classed as an intuitive extrovert. She was not bound by principle and was not loyal. She was somewhat of an opportunist. She was usually happy but quite changeable. She was quickly excitable; she was not inclined to brood or worry. She was rather aggressive.

The patient had many recreative activities. She enjoyed music and the drama, but disliked reading. She hated the movies. She was not particularly religious or inclined to politics. She had little tendency to control her appetites.

This woman is matter of fact and handy with tools. She is unusually active and aggressive for a woman. As a child she was a "tomboy" and spurned dolls. Her two marital experiences were not good, and her whole sexual adjustment was difficult.

The following excerpts further illustrate the point under discussion:

Gastric Ulcer Females.—The following cases are typical of the type mentioned:

CASE 20.—The patient was married at 21 years of age. Her husband died young, leaving her with four small children. By doing waitress and chamber-maid work, she had managed to support the family very well. The educational opportunities were such that she was not fitted to do other work. She said: "I work too fast, my reason tells me one thing and my emotions another. I have never had time for the usual good times of woman." She was never interested in remarrying. She was the youngest child of a large family, and a difficult stepmother situation colored her early childhood.

CASE 21.—The patient was married at 24 to a man younger than herself. This patient showed unusual control over her emotions. Her feeling was suppressed by reason. She assumed a protective rôle toward her husband. She was very proud of her expert tailoring abilities. (This woman was of the thin type, but her general appearance was quite feminine.)

Duodenal Ulcer Female.—The following case is typical of the type mentioned:

CASE 22.—The patient hated the idea of being a girl and so well adapted herself to a male rôle that her brothers were always willing to take her hunting and fishing with them. She spent her spare time in the carpentry shop of her father. She married at 17 years. The family made the match. The marriage was distasteful to her. Her husband died when she was 20 years old and left her with two small children. As a housekeeper in wealthy homes she had supported herself and the children. She had been called on for a good deal of executive work. She claimed that she had many opportunities for remarriage, but had never been interested. Her daughter was a pathetic, flat chested old maid school teacher, who had apparently never been allowed to have much life of her own, but had rather followed the dictates and plans of the mother. The patient was quite masculine in appearance.

If one contemplates the qualities perceived in the morphologic panel and in the case histories and excerpts, it is not difficult to see that the males present a surprising number of feminine attributes and the females much masculinity. These conditions have been so striking and are so closely related to sex reversibility and dualism that it has seemed best to discuss these phenomena separately. The following section deals with the androgynous mosaic and especially with the psychologic reactions that arise within the individual because of it.

THE ANDROGYNOUS MOSAIC

The strange and perplexing aspect of femaleness within the male and maleness within the female is, of course, not new. The circumstance of androgyny has long been recognized, not only by biologists and philosophers, but, generally, by most people. In discussing the matter of sex reversibility and duality within the same person, Oscar Riddle [14] wrote:

> In general it can be said that whenever the "primary" sex characters (gonads) are reversed, the "accessory" and "secondary" characters are reversed also. For the reason that the primary sex character usually develops or differentiates earlier than do the so-called secondary ones, it happens that reversals occur more often and more readily in the secondary than in the primary characters. At once, therefore, we face the hard won fact that genetic (chromosomal) difference normally decides prospective sexuality, primary and secondary; but that this chromosomal difference is not the real or ultimate cause of sex difference—since usable agencies may secure either sex from the same chromosomal complex.

A little further on, after a discussion of the distribution of X and Y chromosomes, the following statement appears:

> The difference in kind is often visible in the sex chromosomes (X and Y); and sex determination normally follows the distribution of X and Y; it is not chromosomes as such, however, but genes carried in all chromosome-antosomes and sex-chromosomes that exercise this influence upon the origin and development of sexuality. This genetic complex, whether prospectively male or female, contains also a numerous minority of genes predisposed to the formation of the opposite sex; cytology has thus discovered and provided a basis for bisexuality in the individual.

In human beings there are plenty of examples of sex reversibility. Thus, for instance, virilism in the female has been described by Gallais,[15] Holmes [16] and others in association with tumors of the suprarenal gland. The observations of Riddle [14] on pigeons and doves, of Finlay [17] on fowls and of Meisenheimer [18] and Hegner [19] on insects add further support to the belief that there is a definite sexuality of the soma which is expressed in the secondary characters of the individual, regardless of the presence or character of the gonad. In this connection, attention may be called to our earlier suggestion [20] that in those maladies in which one sex is definitely more often affected than

14. Riddle, Oscar: Factors in the Development of Sex and Secondary Sexual Characteristics, Physiol. Rev. **11**:63, 1931.

15. Gallais, A.: Le syndrome génito-surrénal, Paris, 1912.

16. Holmes, G.: Quart. J. Med. **18**:143, 1925.

17. Finlay, G. F.: Brit. J. Exper. Biol. **2**:439, 1925.

18. Meisenheimer, J.: Geschlecht und Geschlechter, Jena, Gustav Fischer, 1921, vols. 1 and 2.

19. Hegner, R. W.: The Germ-Cell Cycle in Animals, New York, The Macmillan Company, 1914.

20. Draper, G.: The Influence of Sex upon the Constitutional Factor in Disease, New York State J. Med. **25**:1065 (Dec. 1) 1925.

the other, the selective susceptibility may very well be looked on as a secondary sex character. The effect of this curious arrangement on the behavior of those species which respond, without calculation, to the pressure of instinct is definite enough in respect of the attitude of one sex toward the other. Indeed, when a sex reversal is achieved experimentally, the somatic secondary sex characters always change, but so does the animal's psychology as displayed in modified conduct and demeanor. Thus there seems to be little question that sex reversibility and duality in the individual are biologic facts, not only in the lower animals, but also in man.

In man, however, the situation becomes infinitely complex because of his elaborate psychologic structure. Not only is he forced to make satisfactory (i. e., life-preserving and perpetuating) adaptations to the physical universe, but likewise he is continually driven to the task of establishing and maintaining an adequate adjustment of his personal, inner "man-environment unit." This psychologic unit is composed of his own idealized ego with its satellite emotions and the environment projected by his phantasy. In the life of primitive man, it is clear that physical strength and spiritual determination were the surest guarantees of security amidst the many dangers of his surroundings. Consequently, the virile attributes were especially desirable. They are the qualities that give to their possessors power over both animate and inanimate nature. The individual, man or woman, who holds such power obviously has a better chance of survival than the one who lacks it. If this be true, then maleness must form the biologic foundation on which rests the instinct of self-preservation. In comparison, femaleness is incomplete, inadequate. This conception of the significance of maleness and the relative insignificance of femaleness has an important bearing on many psychologic problems that arise in the lives of human beings, and especially those that relate to the phenomenon of androgyny.

In almost all animal species many more male than female embryos are started. Thus, in the human species, it has been shown that for every 100 aborted female embryos there are 160 males. At term, from 104 to 106 living males are born for every 100 females. But at the end of the first year, there are 103 living females for every 100 males. It would seem, therefore, that the other instinctive urge, namely, that of race preservation, put a higher value on females than on males.

Femaleness thus appears to be essentially concerned with the safety of race or species, just as maleness is with that of the individual or self. But the problems presented to physicians by disease primarily concern the safety of the individual. Possibly it is for this reason that the perception of the female compound of the androgynous mosaic is often so disturbing to human beings. A man who possesses that degree of femaleness

which threatens the authenticity of his essential maleness becomes subject to deep-rooted, unconscious fears lest he fail in his attempt to play successfully the masculine rôle in life. Sometimes the recognition of the magnitude of this female component may have been vaguely or sharply recognized in consciousness, as it was by the patient in case 1. But even in that instance, the consciously presenting or vocalized fear was of homosexuality, although the dreams spoke otherwise. More often the fear of masculine failure has not reached consciousness at all and finds vicarious expression in violent efforts to display unusually virile capacities of mind and body and in the erotic conquest.

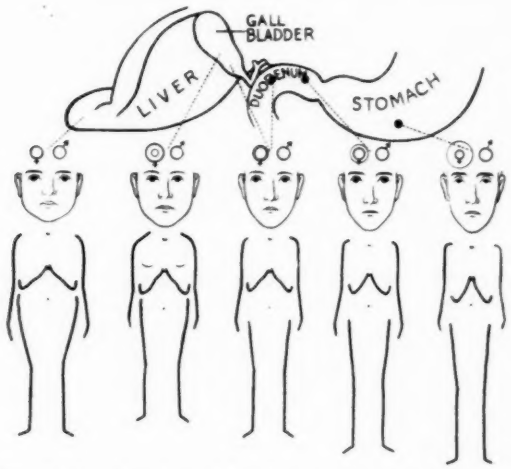

Fig. 8.—Distribution of male and female components in peptic ulcer and gallbladder people.

In the case of the female the mechanism is practically the same. If there is any difference it is more in degree than in kind. The histories and excerpts showed that among the women there was a strong trend toward independence of action in life, desire to dominate and direct the course of others and to assume responsibility. In addition, they all reported a distinct lowering of sexual interest.

Figure 8 presents schematically our conception of the distribution of the male and female component in relation to gallbladder disease and peptic ulcer. It will be observed that the most feministic contours are found in the gallbladder individuals and that these gradually disappear through the series until they are least noticeable in the gastric ulcer. The sex symbols above the figures are intended to suggest the relative proportion of male and female in the individual, and it will be

observed that there is a diminishing amount of femaleness in the direction of the gastric ulcer person. But the psychologic reaction of these persons to their unconscious perception of their female component is apparently in inverse ratio to the actual content as indicated. This increasing reaction, which is actually the fear that the male has for the feminine component, is indicated by the circles with an increasing diameter juxtaposed to the sex symbols. This mechanism is reflected in the increasing ratio of females to males among duodenal, pyloric and gastric ulcer, respectively, which was previously referred to in St. John's [6] report. The figure on the extreme left represents the person with pernicious anemia. This individual is nearest to the neuter or species type. It is referred to the liver because of the relationship between the liver and blood-forming mechanism which has recently been demonstrated. With this brief explanation of the figure the reader will, on completing a perusal of the case histories, be able to perceive further significance in the diagram.

Attention might also be called to the fact that among duodenal ulcers a far greater number of patients begin their symptoms before the age of 25 than is the case among gastric ulcers. Thus Blackford and Dwyer [21] found that in a series of 250 cases 50 per cent of the duodenal group reported that their symptoms began before the age of 25. In the gastric group less than 25 per cent showed symptoms before the age of 25 years. The most natural time in his life for a man to sense the threat of a too great feminine component is at the end of adolescence. It is then that he is approaching the moment when he will have to take his place in the competitive world and begin to assume the full responsibility which falls to the lot of the male. Among the gastric group, in which the female component is less marked, it is not so apt to be appreciated until the full pressure of an adult male's responsibility falls on him.

At this point it is not only of historical interest but also of aid in comprehending these mechanisms to refer to Freud's [22] writings on the subject of human psychosexual development. He pointed out that in very early childhood the clitoris and penis are analogous in respect of their erotogenic sensibility. Furthermore, the evidence of sex differentiation in attitude and behavior appears early in the greater shyness, modesty and timidity of girls. At puberty in boys the urge toward sexual activity and prowess is augmented in association with the rapidly increasing size of the external genital organs and the physical strength of the muscles generally. On the other hand, in girls the onset of

21. Blackford, J., and Dwyer, M.: Peptic Ulcer: A Clinical Study of 250 Cases, Tr. Am. Gastro-Enterol. A. **29**:112, 1927.

22. Freud, S.: Drei Abhandlungen zur Sexualtheorie, ed. 5, Leipzig, Franz Deuticke, 1922; translated by A. A. Brill, New York, 1910.

menstruation and the obvious failure to develop further and convincing evidence of what has been a more or less successful identification comparison with the male increase the protecting walls of shyness and modesty. Evidence of having been outstripped in vigor, not only by demonstration of muscular strength, but also through the symbolism of virile sexuality, is overwhelming. In the face of these handicaps, many young women, especially in this day of general interest in athletics, resent the fact of their femaleness. This attitude is well illustrated by the case of a patient whose menstruation did not begin until she was 19 years old, and who, up until the age of 35, notwithstanding her unusually feminine appearance, still resented being treated chivalrously by men and more than anything else feared lest she play the rôle of clinging vine. Freud's basic observation and theory that the individual's psychologic reaction to life begins as male in both sexes and is subsequently arrested at puberty in the female go far to explain the intense effort of males to repudiate any suggestion of femaleness within them, and of females to strive to achieve and hold some evidence of residual maleness. Adler [23] subsequently seized on this thesis and elaborated it into his new well known concept of the "masculine protest."

The importance of the androgynous mosaic in determining the constitutional reaction to environment is therefore very great. On the one hand, it influences the immediate physical reactions of the individual to his palpable environment, and, on the other, profoundly affects his subjective psychologic interpretations of life experience. The creative force that we blindly call "mother nature" seems to be chiefly occupied with the continuation of the life principle, with the maintenance of species. She is not concerned at all with the fate of the individual. The latter must look out for himself by his own effort. For nature's purpose, then, females, among bisexual forms at least, are evidently more valuable than males. Femaleness displays a lower metabolic rate, is anabolic and represents conservation generally. It follows from this premise that in producing a male creature nature is moving further from her fundamental pattern than when she produces a female; thus the male individual is more widely differentiated from the species type than is the female. For this reason, it is not impossible that males possessing a very high degree of femaleness are more common than females with great masculinity.

Psychologically, however, the individual male cannot accept his female component with equanimity. The main exception to this seems to be in the case of the male of the gallbladder race. The degree of femaleness in such men is expressed very strongly in the soma as well

23. Adler, A.: The Neurotic Constitution, 1912; translated by B. Glueck and J. E. Lind, New York, Moffat, Yard & Company, 1917.

as in the psyche. Consequently, he seems to be less in conflict, and thus better able to accept the feminine component. His disease is anabolic. The significant difference between the males of the gallbladder and ulcer races, therefore, is one of psychic or emotional reaction to the feminine component. The gallbladder male accepts it; the ulcer male denies it. From this conflict arises the fear in the subconscious mind of the potential ulcer patient that when the crucial test comes he will fail to play the masculine rôle successfully. This elemental emotion, which might well be termed the essential male fear, forms a continuously present and active substratum of apprehension. The amount and intensity of that foundation obviously vary depending on the actual balance of the opposite sex qualities within the individual, and also on his constitutional sensitiveness to the threat of the female component.

Superimposed, then, on this chronic layer of anxiety is the acute or precipitating fear occasioned by the transient menace to life, limb or ego. This is produced by the shocks so frequent, for example, in the lives of taxi drivers, bank messengers and persons whose occupations are such that a mistake means the loss of position by dismissal.

But the questions may well be asked whether this androgynous conflict is not present in all human beings, and if so why do not many more, if not all, people have ulcers? Quite obviously the phenomenon of androgyny is common to all persons, although the amount and distribution of the opposite sex component vary. Thus in a primary male the secondary female inclusion may be expressed wholly in one of his four panels of personality, or scattered between two or more. Still more important, however, is the person's subjective psychologic reaction to the feminine attributes. This is determined by his constitutional type. The specific response of a person to an emotion such as fear or anger is as much an expression of his constitution as is his reaction to bacterial or chemical insult.

The mechanisms that have just been discussed are active in the deeper levels of the mind, far below conscious thinking. For this reason they cannot be approached directly by explanation and argument. Some patients can be helped and even cured through the indirect attack of various forms of suggestion therapy or reeducation. But in our experience there are growing indications that in the principles of analytic psychology are to be found the ways to explanation and cure of all the functional disorders of the gastro-intestinal tract. However, a discussion of the relative value of different methods of psychologic diagnosis and therapy does not properly belong in this communication. Rather has the attempt been made to show that an intimate study of the "man-environment unit" may be at least as illuminating as are the investigation and treatment of the diseased organ itself.

SUMMARY

Unlike those medical investigations in which definite proof can be offered, the present study is concerned with phenomena that do not lend themselves to absolute determination. Yet there are important diagnostic and therapeutic implications contained in the correlations of total personality studies with recognized psychologic complexes and certain functions of the endocrine glands and the sympathetic nervous system.

To summarize, then, it may be said that the ulcer race families seem to produce a preponderance of males, and that these males are of the long thin type. Furthermore, not only in their morphology, but also in their psychologic make-up, they display a well marked emphasis on the feminine component of the androgynous mosaic. Fear, which is clearly an important factor in the digestive disturbance of the gastric ulcer race, is of two sorts: First, there is the chronic substratum of anxiety due to the person's constitutional sensitiveness to the threat of the female component. This is the elemental emotion which results in the masculine protest. Second, there is the acute or precipitating fear occasioned by the accident or insult which provides a transient menace to life, limb or ego.

It would seem that the peptic ulcer race was composed of persons of definite constitutional type. These people possess qualities of soma and psyche which can be easily recognized. When the healthy balance of the "man-environment unit" is disturbed, symptoms in the domain of the sympathetic nervous system and gastro-intestinal tract develop. The "man-environment unit" disturbance can often be corrected permanently by the use of appropriate psychotherapeutic methods. Analytic psychology at present seems to offer the best attitude of approach.

EFFECT OF LIGATION OF THE PAROTID DUCT ON THE CARBOHYDRATE METABOLISM OF TOTALLY DEPANCREATIZED DOGS *

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In another study,[1] the results of ligation of the parotid duct on the carbohydrate tolerance of normal dogs were reported. In these animals, it was found that the tolerance for dextrose, as determined by the blood sugar curve following the intravenous injection of dextrose solution, was definitely increased by ligation of the parotid ducts. As a step in the study of the mechanism of this action, the effect of ligation of the parotid duct was determined in a series of totally depancreatized dogs. Mansfeld and Schmidt [2] found that after partial extirpation of the pancreas (Sandmeyer diabetes) the resulting disturbances in carbohydrate metabolism were greatly relieved by ligation of the parotid ducts. In one animal in which the entire pancreas had been removed they were unable to detect any improvement following ligation of the parotid duct. Seelig [3] found that ligation of Stenson's ducts did not prevent animals from dying after pancreatectomy. Extirpation of the pancreas, however, in animals in which the parotid ducts had previously been ligated, did not result in as high blood sugar values as were obtained in those in which the salivary ducts had not been occluded. Furthermore, these animals exhibited better wound healing than did those without ligation of the duct, and they did not suffer the characteristic, rapidly progressive cachexia of pancreatectomized dogs. In a few earlier, inconclusive experiments, we found that ligation of the parotid ducts in no way affected the rapidly downward course of dogs following total extirpation

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1. Zimmerman, Leo M.: Effect of Ligation of the Parotid Duct on the Carbohydrate Tolerance of Normal Dogs, Arch. Int. Med. **49**:409 (March) 1932.

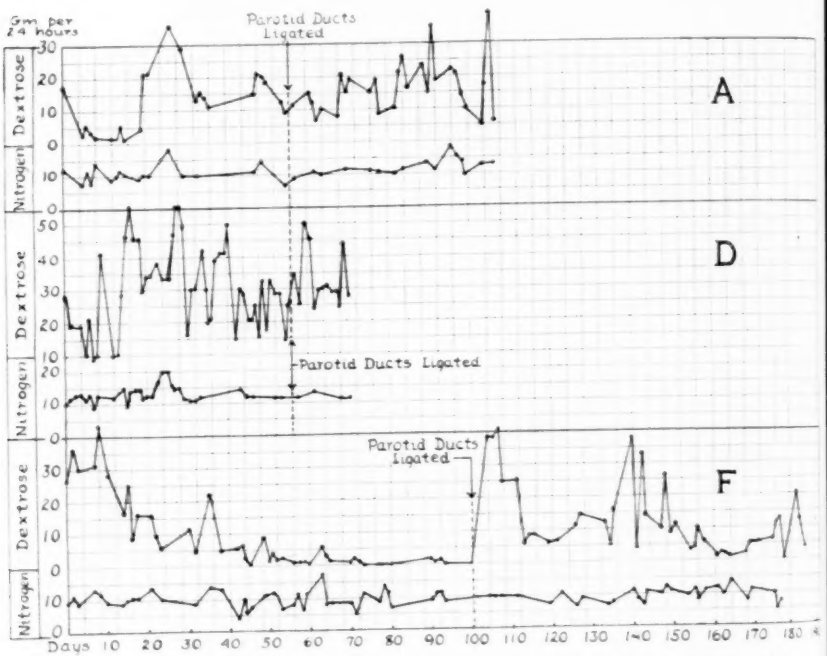
2. Mansfeld, G., and Schmidt, E.: Versuche zu einer operativen Behandlung des Diabetes, Klin. Wchnschr. **7**:1457, 1928.

3. Seelig, S.: Ueber Beziehungen zwischen Parotis, Pankreas, Blutzucker und Diabetes mellitus, Klin. Wchnschr. **7**:1228, 1928.

of the pancreas. In the experiments to be described here, careful metabolic studies were made in a series of three dogs that had recovered following total pancreatectomy. After an adequate period of observation, the parotid ducts were ligated, and the studies were continued.

METHOD

Completely depancreatized dogs were used for this work. The animals were allowed to recover completely from the operative procedure with the aid of insulin,



Curves showing the excretion of dextrose and nitrogen before and after ligation of the parotid duct in three animals, *A*, *D* and *F*.

and presented well healed, noninfected wounds. They were maintained on a meat, sugar, raw pancreas and insulin regimen throughout these experiments. In each case the diet and insulin were kept as constant as possible throughout the entire period of observation. The amount of insulin used in the different experiments was graded, so as to maintain different levels of glycosuria in the different animals. After a control period of from two to three months, both parotid ducts were ligated under a brief ether anesthesia, and observations were continued as before. Dog F was followed for almost three months after the ligation was performed. Twenty-four hour specimens of urine were collected at intervals throughout each experi-

ment and analyzed for nitrogen by the Kjeldahl method, and for dextrose by the Somogyi[4] modification of the Schaffer-Hartmann technic. The results are presented in graphic form in the accompanying chart.

COMMENT

In the accompanying chart, which shows the excretion curves in three animals, both before and after ligation of the parotid duct, it is noted that the dextrose output is fairly uniform. The curve is apparently more constant in the animal that was kept at a low level of glycosuria than in those with a higher excretion of dextrose. The nitrogen output is uniform, and serves as a check for the excretion of dextrose. There is no striking change in the level of glycosuria as a result of the ligation of the parotid duct. It would therefore seem that ligation of the parotid ducts has no effect on the carbohydrate metabolism of totally depancreatized animals.

These results, which coincide with others reported, as mentioned earlier in the paper, would indicate that the factor that increases the carbohydrate tolerance of normal dogs as a result of ligation of the parotid duct is incapable of action when the pancreas has been removed. This suggests that it is not primarily an insulin-like action, but that it operates through the pancreas, possibly in a stimulating or activating manner. The failure of its action in the pancreatectomized animal does not prove, of course, that the operation would be without effect in cases of diabetes in human beings.

CONCLUSIONS

Ligation of the parotid ducts exerts no demonstrable effect on the carbohydrate metabolism of totally depancreatized dogs. The factor that is responsible for the increased dextrose tolerance following ligation of the parotid ducts in normal animals, therefore, probably does not have a direct, insulin-like action, but rather operates through the pancreas as an activating or stimulating agent.

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SUBACUTE BACTERIAL ENDOCARDITIS DUE TO STAPHYLOCOCCUS ALBUS

REPORT OF A CASE *

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It is my endeavor to present the clinical, bacteriologic and pathologic findings as well as the daily progress in a case of subacute bacterial endocarditis due to Staphylococcus albus, with a view toward the further study of the disease caused by this group of bacteria.

The clinical and bacteriologic manifestations of subacute bacterial endocarditis have been carefully studied and described by a large number of clinicians, both in this country and abroad. In a study of 5 cases, Schottmüller [1] found Streptococcus mitior (viridans) as the cause of this type of bacterial endocarditis. In a study of 97 cases of subacute bacterial endocarditis, Horder [2] found 62 due to streptococcus, 19 due to Staphylococcus aureus, 5 to influenza bacilli, 3 to gonococcus and 1 to streptococcus and staphylococcus. Osler's [3] study of 10 cases, in 6 of which cultures of the blood were taken, showed negative results in 3, streptococcus in 1 and staphylococcus in 1. In the exhaustive studies of Libman and Cellar,[4] as well as in Libman's [5] later studies of the atypical forms of subacute bacterial endocarditis, during which positive cultures were obtained, the bacteria most frequently found as the cause was Streptococcus viridans. Lenhartz,[6] in his study of 37 cases, found 19 due to streptococcus, 9 to pneumococcus, 7 to Staphylococcus aureus, 1 to gonococcus and 1 to Staphylococcus albus. Clawson,[7] in a study of 46 cases, found 34 caused by streptococcus, 5 by pneumococcus and 7 by Staphylococcus aureus. In his report on cases of subacute bacterial endocarditis from the Johns Hopkins Hospital, Thayer,[8] found the

* Submitted for publication, July 27, 1931.

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2. Horder, T. J.: Quart. J. Med. **2**:289, 1909.
3. Osler, W.: Brit. M. J. **1**:467, 1885.
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5. Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Arch. Int. Med. **33**:701 (June) 1924.
6. Lenhartz: München. med. Wchnschr. **482**:1178, 1901.
7. Clawson, B. J.: An Analysis of Two Hundred and Twenty Cases of Endocarditis, Arch. Int. Med. **33**:157 (Feb.) 1924.
8. Thayer, William S.: Johns Hopkins Hosp. Rep. **22**:1, 1926.

following groups among the 137 fatal cases that came to necropsy: streptococcus, 60; Staphylococcus aureus, 26; pneumococcus, 26; gonococcus, 19; Staphylococcus albus, 4; pyocyaneus, 1, and anthracis, 1. These figures show that the streptococcus is the type of bacteria that most frequently produces subacute bacterial endocarditis. The bacteria next in frequency is Staphylococcus aureus, with pneumococcus and gonococcus following. Last comes Staphylococcus albus.

REPORT OF A CASE

History.—E. F., a white girl, aged 16, was admitted to the People's Hospital, New York, on Feb. 4, 1931. She had had the ordinary diseases of childhood. Otherwise, the past history was unimportant. About six months prior to admission to the hospital, the patient was working hard and long hours, from 8 a. m. to 10 p. m. About four months before admission, she began to feel weak and became nervous and lost her appetite. She had pains in the joints of all the extremities, but there was no swelling. On Jan. 21, 1931, two weeks before admission to the hospital, the patient was sent to the country, where she contracted a cold and cough with pain in the chest and occasional headaches. She became more pale and nervous. She returned to the city and was admitted to the hospital. The chief complaints on admission were pain in the chest, cough and asthenia.

Physical Examination.—The patient was well developed, markedly pale and somewhat emaciated. The skin was moist and clear; no rashes or petechiae were seen. The pupils were equal and reacted to light and in accommodation; the conjunctivae were clear and pale. The mucous membrane of the mouth was pale, the tongue coated, the pharynx slightly congested and the tonsils small and cryptic. No pus could be expressed from them. The ears were normal. The heart was moderately enlarged; a loud systolic murmer was heard at the apex and was transmitted over the entire cardiac area to the left axilla posteriorly and to the interscapular region. Examination of the lungs revealed normal resonance, vesicular breathing and no râles. The abdomen was soft, with no area of tenderness; the liver and spleen were not palpable. The extremities were normal; the patellar reflexes were normal; there was no Babinski or Kernig sign. The genitals were normal.

Course.—On admission, the temperature of the patient was 102 F.; the pulse rate, 132; the respiratory rate, 24, and the blood pressure 110 systolic and 60 diastolic. The patient appeared comfortable and did not complain of anything except asthenia. Roentgen examination of the chest gave normal results. During the patient's stay at the hospital, the temperature ranged from 99 to 104.2 F., the average being between 101 and 103 F.

February 16: The patient complained of pain in the left forearm. The temperature rose to 103.2 F. Examination showed no areas of redness or swelling. The tenderness was along the muscles of the painful area.

February 19: Physical examination showed the cardiac condition about the same. The spleen was moderately enlarged but not tender, and was felt about 1 inch below the free border of the ribs. No petechiae were found.

February 25: The patient complained of pain in the finger-tips. There was no swelling or tenderness in any of the joints of either hand.

March 4: A transfusion of 350 cc. of blood was given by the Unger method.

March 5: The patient had a slight chill during the night which lasted about two minutes, and she coughed at times. Reexamination gave negative results.

March 14: The patient vomited, appeared drowsy and complained of pain in the joints.

At intervals of a few days thereafter she showed the following symptoms: weakness and pain in the muscles of the right leg, increasing apathy, no desire for food, twitching of the facial muscles and aphasia.

A second transfusion was performed; 400 cc. of blood was given; this had no effect. Her condition became gradually worse; incontinence developed followed by hemiplegia on the right side and dysphagia.

On March 30, the patient went into coma, and petechial hemorrhages appeared on the conjunctiva of both lower eyelids.

Her condition became progressively worse, and she expired on April 2.

Laboratory Data.—Cultures of the blood on February 4, 5 and 17 gave negative results after ninety-six hours. A culture made on February 28 was positive for Staphylococcus albus after ninety-six hours. Positive cultures for the same organism were again obtained on March 11 and 24, after seventy-two hours.

Hospital Chart of Laboratory Observations

Date	Total Red Blood Cells	Hemoglobin, per Cent	Total White Cells	Polymorphonuclears, per Cent	Large Mononuclears, per Cent	Small Mononuclears, per Cent	Basophils, per Cent
February 4	1,920,000	40	12,000	76	..	24	3
5	1,930,000	40	15,500	71	10	19	..
19	2,260,000	45	14,600	88	..	12	..
28	2,250,000	43	14,000	89	..	10	1
				Band Form			
March 3	.....	..	.....	39	..	..	..
5	2,000,000	46	10,200	91	..	9	..
7	3,629,000	37	6,900	90	..	10	..
24	1,700,000	26	6,000	16	..	4	..
30	1,208,000	23	5,300	99	..	1	..

In order to eliminate all possibility of contamination, the culture made on March 24 was taken in the operating room prior to the transfusion of blood.

Daily urinalysis showed an average specific gravity of about 1.022, albumin 4 plus, no sugar and no acetone or diacetic acid. Microscopic examination showed hyaline and granular casts, but no red cells.

Necropsy.—Autopsy was performed on April 2. Cultures from the pericardial fluid showed a growth of colonies of Staphylococcus albus after three days. A culture of valve vegetation showed a growth after seven days. Transplanted smears showed Staphylococcus albus.

The heart, lungs, kidneys, spleen and liver were examined.

Macroscopic examination disclosed numerous petechial hemorrhages seen on the parietal and visceral pericardium. Near the apex of the left auricle there were adhesions between the visceral and parietal pericardium which were easily broken. The pericardial fluid was increased.

There was dilation of the right side of the heart, with hypertrophy of the left. The mitral valves were almost entirely destroyed by ulcerations, and were replaced by fragile vegetations of various sizes. The cusps were fused and narrowed. On the wall of the left auricle there was a small area of vegetation. The other valves were normal.

The pleural cavities were clear. The left lung was adherent to the wall of the chest. There were no areas of consolidation. The right lung was the seat of numerous infarcts, some of which had broken down and were surrounded by red areas of consolidated lung tissue.

The liver appeared normal. The spleen was markedly enlarged, and showed a number of infarcts, some old and healed, others fresh and white.

On section, the left kidney showed scarring from old infarcts.

Microscopic examination of the lungs showed chronic congestion with scattered areas of lobular pneumonia.

The spleen showed congestion and edema, infarction with beginning fibrosis.

The kidneys showed congestion and edema of the tubules.

The heart showed ulcerative endocarditis; the muscles of the heart showed scattered areas of round cell infiltration. No Aschoff bodies were present.

Bacteriologic examination of stained tissues showed all organs to be negative for bacteria, except the vegetation of the valves which contained gram-positive cocci in groups, but no chain formation.

SUMMARY

Clinically, this case bears such close resemblance to the type of subacute bacterial endocarditis caused by the Streptococcus viridans, as described by Libman and Cellar [4] and by Libman [5] in his later studies of the atypical forms, that the clinician may easily be misled in diagnosing this case and classifying it as one caused by the Streptococcus viridans were it not for the blood cultures. There are, however, in this case, a few clinical points which differentiate it from the cases described by Libman.

Although on several occasions the patient complained of pain in the joints and muscles, at no time was there any visible swelling, redness or heat changes in the disturbed parts. There were no corresponding changes in temperature that would be expected with such conditions. At no time during the patient's stay at the hospital could substernal tenderness be elicited. Petechial hemorrhages did not appear until three days before death, although embolic phenomena appeared in other parts of the body.

The appearance of the patient suggested severe anemia, but there was not the *café au lait* color described by Libman.

This case differed clinically and pathologically from the cases described by Thayer.[6] In all of his cases there was a known focus of infection. Of the four cases described, the first was a mixed infection with typhoid intestinal hemorrhages; the second was a case of pulmonary tuberculosis with cavities of the lungs, syphilitic aortitis and chronic valvular lesions; the third was a case of pulmonary tuberculosis and incapsulated interlobar empyema, and the fourth was of acute onset following paronychia with high temperature and all other symptoms of an acute infection. In this case the white blood count was 44,000. The patient died in twenty-three days. In all of his cases, the observations

on the blood and the hemoglobin percentages varied markedly from those of the case herewith reported. The red blood counts ranged from 3,604,000 to 3,761,000. The hemoglobin percentages were between 63.6 and 64.3. In three of the cases, the white blood count was between 8,000 and 10,000. With the exception of one case, the duration was from three to four months. The myocardial changes were insignificant. Pericarditis was not observed. The vegetations in the valves were large, except in the case of typhoid fever.

The case described by Lenhartz [6] varied from the case reported in that the onset was acute, following trauma, and the course was short.

Dr. Held, Dr. Diamond, Dr. Dubovsky and Miss Gold, the laboratory technician, gave assistance and suggestions in this work.

CHOREA GRAVIDARUM

A STATISTICAL STUDY OF 951 COLLECTED CASES, 846 FROM THE LITERATURE AND 105 PREVIOUSLY UNREPORTED

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(Concluded from page 533)

CLINICAL COURSE

Month of Onset of the Chorea.—The available material has been carefully studied with respect to the month of pregnancy in which the chorea first manifested itself. Data on this subject were available in 670 cases. The choreic attack preceded the pregnancy in 38 cases. It developed in the first trimester in 312 cases, in the second in 219 cases and in the third in 101 cases, including 2 cases in which the attack began during labor and 1 case in which it began on the second day post partum. The distribution of the onset by months is graphically indicated in chart 4. By a rather rough approximation, it will be seen that one half of the attacks are initiated in the first trimester, one-third in the second and one-sixth in the third.

Duration of the Attack and Time of Recovery or Death.—More difficulty was experienced with the accuracy of the data on this point than in any other phase of the study, and the figures to be given are approximations in the majority of instances.

Considering first the nonfatal cases, it was found that in 565 pregnancies the chorea ceased ante partum in 167 cases, intra partum in 1 and post partum in 361, and it was reported to have continued indefinitely post partum in 36. The material was also studied with the view of determining whether or not there was any difference in the proportion of patients recovering ante partum or post partum according to the month of pregnancy in which the attack began, but no particular difference was found. It is worthy of note, however, that in only 1 case in which the chorea was present before conception did recovery occur during pregnancy, while in 18 such cases recovery did not take place until after delivery.

There were 118 cases in which recovery from chorea took place prior to delivery and in which a more or less accurate estimation of the duration of the attack could be made. Study of these cases gave the following results: 1 attack lasted two days; 1, one week; 1, two weeks;

1, three weeks; 31, one month; 37, two months; 23, three months; 7, four months; 6, five months; 7, six months; 1, seven months, and 2, eight months, an average duration of two and one-half months. There were 234 cases available for the study of postpartum recovery. The duration of the attacks prior to delivery was as follows: less than one month, 34 cases; one month, 45; two months, 28; three months, 30; four months, 26; five months, 15; six months, 22; seven months, 17; eight months, 17. On assigning an arbitrary value of two weeks for the cases lasting less than one month, there is an average duration prior to delivery of three and three-tenths months. In 132 of these cases, the time elapsing from delivery to recovery was found to be as follows: 1 attack ceased during labor; 1 in three hours; 4 "immediately"; 1 in one day; 5 in a "few days"; 18 in less than seven days; 44 in the second week; 14 in the third week; 15 in the fourth week; 21 in the second month; 3 in the third month; 1 in the fifth month; 2 in one year;

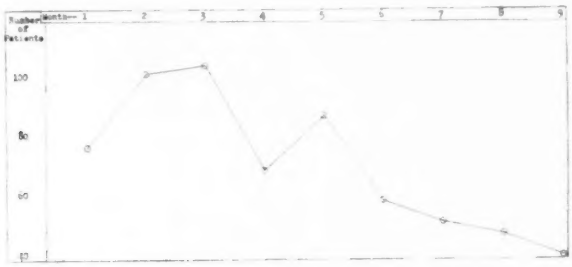

Chart 4.—Month of pregnancy in which choreic attack began in 592 cases.

1 in eighteen months, and 1 in three years. Excluding the cases lasting one or more years, the average postpartum duration of the attacks was about twenty-two days. Eleven additional cases in which the chorea began during pregnancy were reported to have continued post partum indefinitely. This material was also studied to see if any relation could be traced between the duration of the attack before and after delivery, but no such relationship could be found.

In turning attention to the duration of the fatal cases, it is found that 21 patients died undelivered after attacks lasting three, twelve and sixteen days, and one and three weeks in 1 case each; one month in 5 cases; two months in 7 cases, and three months in 4 cases; thus, the average duration of these twenty-one attacks was one and one-half months. In 41 cases terminating fatally post partum, the antepartum duration of the choreic attacks was two days in 2 cases; less than one month in 12 cases; one month in 9 cases; two months in 7 cases; three months in 6 cases; four months in 3 cases, and six and seven months

in 1 case each, an average antepartum duration of one and six-tenths months. In 24 cases terminating fatally postpartum, the interval between delivery and death was one day or less in 5 cases, two days in 9 cases; three, five, six, eight, ten, eleven, twelve, fourteen and a "few" days in 1 case each and one month in 1 case. In the last case, the chorea ceased two weeks postpartum, but the patient died of acute endocarditis two weeks later. On eliminating this case and the one lasting a few days, in 22 cases the average time elapsing between delivery and death was about four days.

From these figures it will be seen that the average duration of attacks terminating during pregnancy in either recovery or death is two and one-half and one and one-half months, respectively; the average antepartum duration of attacks terminating in postpartum recovery or death is three and three-tenths and one and six-tenths months, respectively, and the average time elapsing between delivery and postpartum recovery or death is twenty-two and one-tenth and four and one-tenth days, respectively.

These findings may be compared with those of the report of the British Collective Investigation Committee (Mackenzie) for ordinary chorea. Their data covered the duration of 398 cases, of which 71 lasted less than one month, 133 between one and two months, 95 between two and three months, 44 between three and four months, 32 between four and six months and 23 over six months. For comparison with the cases during pregnancy, these figures represent an approximate average duration of between two and three months. It will be seen that the fatal pregnant cases tend to run a shorter course than this, that the cases in which recovery occurs during pregnancy coincide closely, and that, as might be expected, the cases in which postpartum recovery occurs average approximately twice the duration of the controls. There is certainly no striking divergence between the pregnant and the non-pregnant cases to be detected here.

Chorea Recurring in More than One Pregnancy.—Repeated attacks of chorea, the data on which are given in table 1, are of considerable interest and importance. There were 253 choreic pregnancies in 99 patients; 69 patients had 2 choreic pregnancies, 18 had 3, 7 had 4, 4 had 5 and 1 had 13, an average of 2.5 choreic pregnancies for each patient. The distribution of these in the various pregnancies is given in table 8.

With respect to the course of the chorea in these cases before and in the interval between pregnancies, it is interesting to note that in about two thirds of the 99 cases the reports were sufficiently accurate to show the complete cessation of the chorea between pregnancies, and this was true with proportionate frequency in the cases giving a history of chorea before the first pregnancy and those giving none. It is also of interest to note that in the case of one patient (186, table 1) who had

never had chorea prior to pregnancy the disease continued post partum, complicated 3 pregnancies and, apparently, continued indefinitely after the third. In another case the patient (199, table 1) had never had chorea or rheumatism before the attack of chorea in her first pregnancy. The intervals between the first 3 pregnancies were free from chorea, although it recurred in all. Following the third pregnancy the chorea continued, complicated the fourth pregnancy, and then continued until the patient's death at 68 years of age. Altogether there were 16 instances in which chorea occurred for the first time during pregnancy, was absent in the interval between and recurred in subsequent gestations; in 3 instances, 5 times.

TABLE 8.—*Distribution of Chorea in Various Pregnancies in Same Patient*

Numerical Order of Pregnancies Complicated by Chorea	Number of Cases
First and second	51
First and third; second free from chorea	2
First and fifth; second, third and fourth free from chorea	1
First and thirteenth; others free from chorea	1
Second and third; first free from chorea	5
Second and third; first unknown	1
Second and sixth; others unknown	1
Second and one other, number unknown	1
Third and fourth; first and second free from chorea	1
Third and fourth; first and second unknown	1
Two pregnancies; order unknown	4
First, second and third	12
First, second and fourth; third free from chorea	3
Second, third and fourth; first free from chorea	1
Third, fourth and fifth; first and second free from chorea	1
Three pregnancies; order unknown	1
First, second, third and fourth	5
First, second, fifth and sixth; third and fourth free from chorea	1
Four pregnancies; order unknown	1
First, second, third, fourth and fifth	4
First to thirteenth, inclusive	1

The Effect of Chorea on Pregnancy.—This may be studied from the data in 646 cases. In 314 of these, or 48.6 per cent, pregnancy was uninterrupted and was terminated by spontaneous labor at term. Of the remaining 332 cases, pregnancy was artificially terminated in 171 instances and spontaneously prematurely in 161. The spontaneous interruptions were caused by premature labor in 63 cases, by abortion in 64 cases, occurred at an unknown period of pregnancy in 1 case, by rupture of an ectopic pregnancy in 1 case, and by death of the mother undelivered in 32 cases.

SYMPTOMS

Movements.—It will be unnecessary to go into any detailed consideration of the symptoms. The characteristic hypermotility and incoordination are pathognomonic and, as is pointed out by many observers, differ in no particular and are indistinguishable from those of Sydenham's chorea. The movement is mostly general. In the more severe

cases the patient is constantly in motion, and the incoordination is so extreme that she is absolutely incapable of doing anything for herself. During sleep the movements usually cease.

Fever.—The disease is usually afebrile. Fever, when it does occur, is of ominous significance, and hyperpyrexia may occur; the temperature was 109.6 F. in 1 fatal case and 108 F. in another, with recovery.

Blood Pressure.—The blood pressure is not altered. In 14 different observations, the systolic range was from 136 to 99.

Urine.—The condition of the urine was mentioned in 97 cases; albumin was present in 42 and absent in 55 instances. The presence of casts is occasionally noted.

Blood.—Blood cultures were negative in 3 instances, and in 1 Staphylococcus aureus was isolated. The chemical status of the blood is reported to have been normal in 1 observation. In the febrile cases, a leukocytosis seems to be generally present; in 8 observations the range was between 28,500 and 8,000.

On comparing these symptoms with those of Sydenham's chorea, it will be seen that the characteristic hypermotility and incoordination are identical. Further, there are present no symptoms or laboratory findings that in the slightest degree indicate the presence of any ordinary toxemia of pregnancy, with the possible exception of the albuminuria, which, however, is frequently noted in an otherwise normal pregnancy and would be expected to be present occasionally in a condition of a presumably infectious origin.

COMPLICATIONS

The most frequent complications are acute psychoses, probably usually of the intoxication exhaustion type, acute endocarditis and acute rheumatic fever, all of which are identical with those of Sydenham's chorea and are considered more in detail elsewhere. Eclampsia occurred in 6 cases, which, considering the fact that 320 pregnancies were definitely stated to have gone to full term, would seem to be without special significance. Three cases were complicated by hysteria and 2 by epilepsy. In 1 fatal case there were convulsions followed by coma and hemiplegia, probably of embolic origin.

DIAGNOSIS

The diagnosis offers no difficulties and is usually self-evident. Hysteria might occasionally have to be eliminated, as in the case of pseudochorea of hysterical origin reported by Marshall. Royston considered 1 of his cases to be possibly one of pseudosclerosis. Roques, in a recent article entitled "Epidemic Encephalitis in Association with Pregnancy, Labour and the Puerperium," devoted 113 pages to an

exhaustive consideration of this subject. His study of 21 cases has led him to differentiate definitely between epidemic encephalitis in pregnancy and chorea gravidarum. He stated that the latter is characterized by a previous history of chorea or rheumatism or both, rheumatic nodes, cardiac complications, a greater tendency to spontaneous interruption of pregnancy and the occurrence earlier in pregnancy and more frequently in primiparae. He also gave the mortality of encephalitis complicating pregnancy as 42 per cent in 170 cases, which, as will be shown later, is almost 3 times greater than that of chorea gravidarum.

PROGNOSIS

In table 9, the mortality rates for various groupings of the cases are presented in such form that they may be seen at a glance. These findings will now be considered in detail.

General Mortality.—Figured on the basis of the number of deaths in persons having 1 or more choreic pregnancies, the results were 613 recoveries and 136 deaths, a mortality rate of 18.1 per cent in a total of 749 patients. In these 749 patients, for whom the result was known, there occurred a total of 902 reported pregnancies, and in these the patients survived in 766 instances and died in 136, a mortality rate of 15 per cent for pregnancies. These rates are based on a series of cases almost twice as large as any previously collected and one from which, in marked contrast to most previous series, all duplication has been eliminated. It is interesting to observe, therefore, that they indicate a general prognosis less gloomy than the estimates heretofore usually given, which have ranged around 25 to 33.33 per cent. Further study of the figures tends to reveal an even better prognosis.

Mortality Considered Chronologically.—Thus when the cases are arranged in three groups, according to the date of their reporting, namely, those reported prior to 1880, from 1880 to 1899, inclusive, and from 1900 to date, periods roughly corresponding to what may be termed the preantiseptic, antiseptic and aseptic eras in obstetrics, we find a steady decline in the mortality rates, as follows: preantiseptic era, 124 pregnacies, with 31 deaths, a mortality rate of 25 per cent; antiseptic era, 237 pregnancies with 36 deaths, a mortality rate of 15.1 per cent, and aseptic era, 541 pregnancies with 69 deaths, a mortality rate of 12.7 per cent.

Mortality in Relation to the Previous History Regarding Chorea and Rheumatism.—It is interesting to find how figures based on this large series of cases lend support to the opinion so frequently expressed, particularly in the French literature, that chorea in more than 1 pregnancy, or in a patient giving a history of chorea before pregnancy, is less fatal than the single isolated attack that constitutes the first choreic

seizure. It is, of course, evident that in order to have chorea in more than 1 pregnancy the patient must survive it in at least 1, but, on the other hand, it might be possible and even might be expected, *a priori*, that more patients would ultimately die after several attacks than after one. This is not borne out by the facts, which show 10 deaths in 94 patients having 2 or more choreic pregnancies, a mortality rate of 10.6

TABLE 9.—*Comparative Mortality Rates for Various Groups of Cases*

	Total No. of Cases	Total Lived	Total Died	Mortality Rate
General mortality:				
By individuals	749	613	136	18.1
By individuals, two or more choreic pregnancies for each	94	84	10	10.6
By pregnancies	902	766	136	15.0
Mortality chronologically:				
Prior to 1880—preantiseptic era	124	93	31	25.0
1880 to 1899, inclusive—antiseptic era	237	201	36	15.1
1900 to date—aseptic era	541	472	69	12.7
Mortality in relation to previous history of chorea and rheumatism:				
History of chorea prior to first choreic pregnancy	219	203	16	7.3
No history of chorea prior to first choreic pregnancy	177	145	32	18.0
History of rheumatism prior to first choreic pregnancy	135	125	10	7.4
No history of rheumatism prior to first choreic pregnancy	229	198	31	13.5
History of both chorea and rheumatism prior to first choreic pregnancy	95	89	6	6.3
History of neither chorea nor rheumatism prior to first choreic pregnancy	110	89	21	19.0
Mortality in relation to age by hemidecades:				
15 to 19 inclusive	138	119	19	13.7
20 to 24 inclusive	324	267	57	17.5
25 to 29 inclusive	122	97	25	20.4
30 to 34 inclusive	34	28	6	17.6
35 to 39 inclusive	9	8	1	11.1
Mortality in relation to time of onset of the chorea in pregnancy:				
Chorea present before pregnancy	34	34	0	0
Onset of chorea in first trimester	292	244	48	16.4
Onset of chorea in second trimester	207	173	34	16.4
Onset of chorea in third trimester	98	79	19	19.3
Mortality in relation to psychotic complications	49	41	8	16.3
Mortality in relation to fever	26	3	23	88.4
Mortality in relation to the manner of termination of pregnancy:				
Spontaneous terminations of pregnancy:				
At term	312	306	6	1.9
By premature labor	63	55	8	12.6
By abortion	64	49	15	23.4
By rupture of ectopic pregnancy	1	1	0	0
Total of spontaneous premature terminations	128	105	23	17.9
By death of patient undelivered	32	0	32	100.0
Total of spontaneous premature terminations, including deaths undelivered	160	105	55	34.3
At an unknown period of pregnancy	1	0	1	100.0
Total of all spontaneous terminations, excluding deaths undelivered	441	411	30	6.8
Total of all spontaneous terminations, including deaths undelivered	473	411	62	13.1
Artificial terminations of pregnancy:				
By induction of labor at term	6	3	3	50.0
By induction of premature labor	37	27	10	27.0
By induction of abortion	94	68	26	27.6
By induction at an unknown period	5	2	3	60.0
Total of all cases of induction	142	100	42	29.5
By vaginal hysterotomy	11	8	3	27.2
By abdominal hysterotomy	9	6	3	33.3
By accouchement forcé	7	0	7	100.0
By vaginal hysterectomy	2	0	2	100.0
Total of all cases of operative delivery	29	14	15	51.7
Total of all artificial terminations of pregnancy	171	114	57	33.3
Mortality chronologically; artificial terminations of pregnancy:				
Prior to 1880—preantiseptic era	4	2	2	50.0
1880 to 1899, inclusive—antiseptic era	39	24	15	38.4
1900 to date—aseptic era	128	88	40	31.2
Fetal mortality	537	268	269	50.9

per cent. In a group of 219 cases giving a positive history of an attack of chorea prior to any choreic pregnancy, there were 16 deaths, a mortality rate of 7.3 per cent, with which there may be contrasted a rate of 18 per cent in a group of 177 patients whose histories failed to disclose any chorea previous to the attack during pregnancy.

In 135 pregnancies in which there was a definite history of previous rheumatism, there were 10 deaths, a mortality rate of 7.4 per cent, with which may be contrasted a rate of 13.5 per cent in a group of 229 pregnancies in which the histories positively denied any previous rheumatism. In the group of 95 cases giving a history of both chorea and rheumatism previously there were 6 deaths, a mortality rate of 6.3 per cent, with which may be contrasted a rate of 19 per cent in a group of 110 cases giving a history of neither chorea nor rheumatism.

It will be seen from these findings that there is a definitely lessened mortality in patients who have had chorea or rheumatism previously and a still lower rate in those who have had both. In seeking the explanation for these facts, the most obvious recourse would seem to lie in the direction of some immunologic mechanism—the explanation is difficult on any other hypothesis.

Mortality in Relation to Age.—It will be seen from table 9 that in the first three hemidecades of sexual maturity the mortality increases with the patient's age, while in the fourth and fifth it drops sharply, the exact mortality rates being as follows: 15 to 19, inclusive, 138 cases, with a mortality of 13.7 per cent; 20 to 24, 324 cases, with a mortality of 17.5 per cent; 25 to 29, 122 cases, with a mortality of 20.4 per cent; 30 to 34, 34 cases, with a mortality of 17.6 per cent, and 35 to 39, 9 cases, with a mortality of 11.1 per cent. The rise in the rate for the first three hemidecades seems to be quite definite and what might be expected from the generally accepted fact that the mortality of ordinary chorea is less in children than in adults. The sudden drop in the next two hemidecades is even more definite and, at first glance, would seem to be an unexpected finding. It might be explained, however, by considering two points, namely, that at these more advanced ages none of the women have had previous chorea either with or without association with pregnancy, which, as we have seen, tends to diminish the mortality and, also, that there is more likelihood of error in a diagnosis of chorea gravidarum made at this time of life, when ordinary chorea is so rare as to be a medical curiosity.

Mortality in Relation to the Time of Onset in Pregnancy.—The data available for the study of this subject are from a total of 631 cases, and the results obtained were as follows: onset of chorea before pregnancy, 34 cases with no deaths; onset in first trimester, 292 cases with 48 deaths, a mortality rate of 16.4 per cent; onset in second tri-

mester, 207 cases with 34 deaths, a mortality rate of 16.4 per cent; onset in third trimester, 98 cases with 19 deaths, a mortality rate of 19.3 per cent. It will be seen that there is so little difference in the mortality rates for the various trimesters of onset of the chorea that the conclusion would appear to be justified that this factor is without influence. The striking absence of mortality in the group of 34 cases in which the onset of the chorea antedated the pregnancy is in line with the previously noted lower mortality rate in cases giving a history of previous chorea and is probably to be explained through the establishment of a relative immunity before conception.

Mortality in Relation to the Manner of Termination of the Pregnancy.—For this study data were available in a total of 644 pregnancies. As might be expected, the most favorable manner of termination is by spontaneous labor at term. In 312 such cases there were only 6 deaths, a mortality rate of 1.9 per cent. In 63 cases with spontaneous premature labor there were 8 deaths, a mortality rate of 12.6 per cent, and in 64 cases of spontaneous abortion there were 15 deaths, a mortality of 23.4 per cent. Altogether, including the case in which recovery occurred following the spontaneous rupture of an ectopic pregnancy, there were 23 deaths in 128 cases in which pregnancy was spontaneously prematurely interrupted, a mortality of 17.9 per cent. If, however, we add to these figures 32 patients who died undelivered we have a group of 160 cases in which pregnancy was terminated by the death of the woman undelivered, or by spontaneous premature labor or abortion, with a total of 55 deaths, a mortality of 34.3 per cent. If we include the cases of spontaneous labor at term and 1 fatal case with a spontaneous termination of pregnancy at an unstated period, there is a group of 473 cases in which the pregnancy was not artificially interrupted; of these, 62 died, giving a mortality rate of 13.1 per cent for conservative management of the complicating pregnancy.

Turning now to the cases in which pregnancy was artificially terminated at varying periods and by various methods, we find as follows: In 6 cases in which labor was induced at term, there were 3 deaths, a mortality rate of 50 per cent; induction of premature labor, 37 cases with 10 deaths, a mortality rate of 27 per cent; induction of abortion, 94 cases with 26 deaths, a mortality rate of 27.6 per cent; induced interruption, period not stated, 5 cases with 3 deaths; vaginal hysterotomy, 11 cases with 3 deaths, a mortality rate of 27.2 per cent; abdominal hysterotomy, 9 cases with 3 deaths, a mortality rate of 33.3 per cent; accouchement forcé, 7 fatal cases; vaginal hysterectomy, 2 fatal cases. Altogether, therefore, we have a group of 171 cases in which pregnancy was artificially terminated, with 57 deaths, a mortality rate of 33.3 per cent. A critical examination of the case reports in this

group with the view of determining the number of deaths directly or indirectly due to postpartum infection immediately disclosed the impossibility of arriving at any definite figures. It may be said, however, that there is definite evidence that infection played an important part, and this is borne out by a chronological grouping of the cases, which shows 4 pregnancies artificially terminated prior to 1880, with 2 deaths, a 50 per cent mortality; 39 cases from 1880 to 1899, inclusive, with 15 deaths, a 38.4 per cent mortality, and 128 cases from 1900 to date, with 40 deaths, a 31.2 per cent mortality.

There can be no question that the medical profession has shown little or no tendency toward an unwise radicalism in resorting to therapeutic abortion or induction of premature labor in handling chorea gravidarum; on the whole, one gets the impression that the cases so handled have been wisely selected. This being granted, and taking a mortality of 31.2 per cent as representing what may be expected from this procedure, under modern conditions, that is, in the group artificially terminated since 1899, we find for comparison a mortality rate of 17.9 per cent in 128 cases in which there was a spontaneous premature interruption of pregnancy. It would seem only fair, however, to add to this latter group the 32 cases in which the pregnancy was terminated by the death of the mother undelivered, resulting in a mortality rate of 34.3 per cent. Thus it will be seen that in a group of 288 cases serious enough to result in the death of the mother undelivered or in spontaneous premature interruption of pregnancy, on the one hand, and to indicate to the physician the advisability of artificial, aseptic termination of pregnancy, under modern conditions, on the other, we find a difference in mortality of only 3.1 per cent in favor of intervention.

Mortality in Relation to Psychotic Complications.—Acute mania and other psychoses, delirium, etc., are noted as complicating the choreic pregnancy in 51 cases; in 49 of these in which the result for the mother is given, there were 8 fatalities, a mortality rate of 16.3 per cent. This is so little in excess of the general rate for choreic pregnancies, 15 per cent, that it would seem to indicate a less gloomy prognosis for this complication than is generally conceded in the literature. In several of these cases, however, the psychoses continued post partum, and in some instances the patients ultimately died in hospitals for the mentally defective.

Mortality in Relation to Fever.—It is to be regretted that the majority of the reports are so fragmentary as to make exact deductions difficult on many points; this applies to the incidence of fever. In many cases the context clearly indicates that fever must have been present, yet it is not mentioned. There is a group of 27 cases, however, in

which the presence of fever is specifically mentioned, or, from the context, it is evident it must have been present during the choreic attack. Of 26 of these patients for whom the result was known, 3 lived and 23 died, a mortality rate of 88.4 per cent. This finding strongly confirms the statement of French and Hicks that fever is of the gravest prognostic import.

Fetal Mortality.—The fate of the fetus was either mentioned or could be safely inferred from the context in 537 cases; it survived in 268 instances and died in 269, a fetal mortality rate of 50.9 per cent. A detailed study of these figures seems unnecessary. In about 200 of the 269 fetal fatalities, the pregnancy was interrupted either spontaneously or artificially before the period of viability, or the woman died undelivered. In 79 cases of spontaneous or induced premature labor in which the fate of the child was mentioned, there were 37 deaths. It will be seen, therefore, that prematurity is decidedly the predominating factor in the large fetal mortality rate.

Two babies born with chorea promptly recovered.

There has been a tendency in the literature to differentiate chorea gravidarum from Sydenham's chorea because of its supposedly higher mortality. It will be seen from the mortality statistics just presented that the rate is not nearly so high as has generally been given and that, since 1900, it has been 12.7 per cent. In speaking of the high death rate of chorea during pregnancy, Dakin pertinently said: "Whether this is due altogether to the existence of pregnancy or whether the danger is common to all adults whether pregnant or not, the present cases are not sufficiently numerous to determine; but it is usually believed to be more dangerous to those in the gravid condition." He reported from St. George's Hospital, London, 2 deaths from chorea in 18 nonpregnant women, and Mackenzie reported 1 death in 77 such cases, a total of 3 deaths in 95 cases, a rate of 3.1 per cent. This may be compared with Mackenzie's rate of 1.8 per cent in 432 cases of Sydenham's chorea without pregnancy, but including males and females of all ages. From these figures it would seem that Dakin's question must be answered to the effect that Sydenham's chorea is appreciably more dangerous in the nonpregnant woman than in the child, but that adult chorea is from three to four times more fatal with pregnancy than without it. This, however, is certainly insufficient ground on which to base a differentiation between these two types of chorea. Many examples immediately come to mind, notably that of influenza, illustrating the increased mortality of certain diseases during pregnancy. It must also be borne in mind that the pregnant woman with chorea has, in addition to the hazard of the disease, all the dangers incident to a pregnancy predisposed to premature interruption, spontaneous or

induced. These hazards of pregnancy are undoubtedly responsible for some but not all of the increased mortality. It would seem reasonable to believe that the factors responsible for the remaining increase must be sought in some breakdown of resistance comparable to what may be believed to occur in influenza.

Dakin's additional statement that chorea gravidarum "is certainly much more common in adult women who are pregnant that in those who are not" is not borne out by combining his own and Mackenzie's statistics, which show that of 109 cases of chorea in women of childbearing age, 14 were pregnant and 95 were not. These figures are of importance in showing that pregnancy is by no means the only etiologic factor responsible for chorea in the adult.

TREATMENT

The consideration of treatment naturally divides itself into the question of the treatment for the chorea and the proper management of the pregnancy.

The former of these subjects will first be briefly reviewed from the historical standpoint. The use of chloroform by inhalation with the idea of controlling the hypermotility would seem to be the worst possible procedure. Several authors pride themselves on their faithfulness in continuing this for days, relays of medical students being employed to render it possible. The last case in which such treatment was used was as late as 1906. The result was 7 deaths and 1 recovery in 8 such cases. In the same category is the use of very large doses of morphine. There is good evidence for believing that an overdose of morphine was directly responsible for 1 fatality and for suspecting that it contributed to a few others. The older idea of a reflex origin of the chorea is evidenced by such procedures as applications of iodine to the cervix, or its dilatation, incision of the hymen for the relief of dyspareunia and excision of a urethral caruncle, all of which were believed to have been beneficial and even to have produced cures. Much more rational would seem to be the clearing up of foci of infection by tonsillectomy or the extraction of septic teeth, reported to have been of benefit in a few cases. Haneborg thought he got great benefit from the use of thymus gland in 1 case. Arsphenamine or sodium cacodylate were used in a few cases, apparently merely as a more modern method of administering arsenic. Magnesium sulphate intramuscularly was used in 1 fatal case. On the hypothesis of a pregnancy toxemia, blood serum from a pregnant woman was employed in 3 cases, 2 of which were fatal. Selitzky employed repeated injections of normal horse serum in 3 cases with no deaths.

In looking at the subject from the point of view of modern knowledge of chorea or, possibly, more truthfully, admitted lack of

knowledge, and in accepting as a working basis the hypothesis of the absolute identity of chorea gravidarum with Sydenham's chorea, we may now consider the best modern management of both the chorea and the pregnancy.

With respect to the chorea, it would seem to be safe to admit that we are without any treatment that even approaches specificity and are therefore reduced to a purely symptomatic therapeusis. It is certainly extremely doubtful if the time-honored use of arsenic, either as solution of potassium arsenite or in more modern form, has much effect on the disease, and personally we believe the same may be said for the salicylates. Shaw, of Manchester, claimed good results from large doses of thyroid, which, however, we believe may be equally attributed to the sanity and conservatism of the balance of his method of management. As has been stated, he and also Pinard and Rudaux hold practically identical views in attributing the chorea of pregnancy to gestational toxemias, and, based on this assumption, they advocate rest, isolation, promotion of elimination and a milk diet. The last two authorities employ chloral to effect a depressant action on the nervous system. While the evidence here adduced would seem to justify the conclusion that their etiologic assumption is without any sound basis, their treatment would seem admirably to meet most of the requirements of the situation in the present state of knowledge, and certainly no other method yields better results. The matter of diet is probably open to some question, and one that was bland, nutritious and easily digested, with an abundance of fluid, would probably be more rational than milk alone. Hypnotics other than chloral are, of course, available, particularly the substitution products from barbituric acid. In our own case the judicious use of morphine was certainly helpful in gaining rest and quiet, but Wall and Andrews are undoubtedly right in warning against large doses of these potent drugs. Another important indication to be met is preventing the patient from injuring herself by accidental falls and blows.

When these simple measures fail to bring about improvement, or even to arrest the course of the disease toward greater and greater severity, the question of therapeutic abortion must be met. It is difficult to determine on a fair standard of comparison between the results of intervention and nonintervention as shown by these statistics. A group of 473 cases in which pregnancy was not artificially terminated gave a mortality of 13.1 per cent as against a rate of 33.3 per cent for a group of 171 cases in which it was so terminated. The first group, however, includes 312 pregnancies that progressed to full term, with a mortality of only 1.9 per cent: in these cases the chorea, quite obviously, was in a mild form. It would seem fairer, therefore, to make the comparison between the group of 160 cases in which the pregnancy was spontane-

ously terminated prematurely or resulted in the death of the woman undelivered and the group of 171 cases with artificial terminations; these two groups may be considered as equally made up of the more serious and fulminating cases. The respective mortality rates are 34.3 and 33.3 per cent, a balance in favor of intervention of only 1 per cent. The latter group, however, contains 7 fatal cases in which accouchement forcé was employed, 2 fatal cases in which vaginal hysterectomy was performed and 6 fatal cases of 20 in which the delivery was by vaginal or abdominal hysterotomy. Since the judgment shown in the selection of these methods of procedure would seem open to considerable question, we have eliminated them, and thus have remaining a group of 137 cases in which pregnancy was terminated by induction of labor, prematurely or at term, or therapeutic abortion. In table 10 we have made a chronological comparison between the respective mortality rates resulting from intervention and nonintervention in these two groups.

TABLE 10.—*Chronological Comparison of Mortality Rates with and without Therapeutic Abortion or Induced Premature Labor* *

	Without Intervention				With Intervention			
	Total No. of Cases	Total Lived	Total Died	Mortality Rate	Total No. of Cases	Total Lived	Total Died	Mortality Rate
Prior to 1880	35	13	22	62.8	3	2	1	33.3
1880 to 1899, inclusive	43	30	13	30.2	37	24	13	35.1
1900 to 1919, inclusive	43	30	13	30.2	33	21	12	36.3
Since 1919	39	32	7	17.9	64	51	13	20.3

* Cases going to full term and operative deliveries have been excluded.

Study of these figures discloses, we believe, only two generalizations that may safely be made. First, that since 1919 there has been a sharp decline in the mortality rate both with and without intervention, and, second, that, excluding the 3 cases in the intervention group prior to 1880 as being too small a number to justify comparison, the group with intervention shows a 6.1 to 2.4 per cent greater mortality. From the statistical point of view, therefore, it will be seen that there is no evidence favoring the interruption of a pregnancy complicated by chorea.

Statistical evidence alone, however, is notoriously untrustworthy, and it is thought, therefore, that the question of intervention or nonintervention should be considered further in the light of the evidence adduced in this paper as to the true relationship between the pregnancy and the complicating chorea. We think that it has been conclusively demonstrated that chorea is not a direct complication of pregnancy, but that either the association is a purely accidental one, or, possibly more frequently, the pregnancy acts by reducing resistance to a disease previously present in latent form. The situation would seem to be most comparable to the occurrence of pregnancy in a person with latent or

inactive tuberculosis. In deciding whether or not to intervene, other factors entering into the prognosis should receive careful consideration: on the one hand, the undoubted tendency of pregnancy to prolong the attack, the clinically well attested likelihood of prompt recovery post partum and the triply or quadruply greater mortality during pregnancy; on the other, the lack of mortality in the cases in which the onset of the chorea precedes the pregnancy and the uniformly favorable prognosis in cases giving a history of a previous attack of chorea or rheumatism, or both. We get the impression that the time of intervention has a direct bearing on its efficacy, and that little may be hoped from therapeutic abortion undertaken in the presence of high fever, leukocytosis, petechiae of the skin and other evidences of active infection. One might as well expect favorable results from therapeutic abortion in such acute medical complications as influenza, typhoid, pneumonia or acute endocarditis. Because of this reasoning, we do not accept these symptoms as indications for intervention, as advocated by Pinard and, also, by LePage, and would consider them as best treated expectantly, for we know of no analogous situation in which intervention would be considered as indicated, and the result of intervention under these circumstances, as may be seen from table 1, is almost uniformly fatal. If this logic is sound, it necessarily follows that the time for intervention, if at all, is before such symptoms develop. If, then, despite a thorough trial of a treatment admirably summed up by Wall and Andrews as consisting of "rest, seclusion, careful feeding and gentle discipline," to which it would seem safe to add the judicious use of nerve sedatives, there is a steady progression in the intensity of the disease with constant and violent movement, incoordination of the muscles of speech and deglutition and intractable insomnia, and particularly if psychotic disturbance becomes evident, interruption of pregnancy should be seriously considered. As to the method of election, the results in this series speak eloquently. It would seem evident that under the circumstances involved there will always be time to employ the induction of abortion or premature labor rather than some form of operative delivery, and the advisability of this choice is evidenced by a mortality of 51.7 per cent in 29 cases delivered by vaginal hysterectomy, vaginal and abdominal hysterotomy and accouchement forcé. Exceptions to this rule might be noted in cases in very early pregnancy, in which a simple curettage would suffice, or, in the case of repeated choreic pregnancies, in which the abdominal route might be selected in order to effect sterilization.

SUMMARY AND CONCLUSIONS

This paper is a statistical study based on an analysis of the available data of 951 choreic pregnancies occurring in 797 persons, much the largest collection of cases thus far assembled. One case was personally

observed by us, and the remainder were collected from the literature or through the medium of a questionnaire sent to more than 500 American obstetricians.

The disease is very rare: In 270,825 obstetrical hospital admissions from Europe, America and Australia, the incidence was 1 case in 2,275 pregnancies; in 115,554 similar admissions in the United States, the incidence was 1 case in 3,501, which undoubtedly gives an exaggerated idea of its frequency here, since of 170 obstetricians replying to our questionnaire, 113 had never seen a case.

Our study has led us to the definite conclusion that the chorea occurring during pregnancy is identically the same disease as Sydenham's chorea in adolescents, modified slightly, in certain respects, by its association with pregnancy. This opinion we believe to be positively supported by the following facts:

1. Women attacked are predominantly in the youngest age group of sexual maturity and are mostly primiparae.

2. More than one half of them give a history of a previous attack of an ordinary chorea, more than one third of them of a previous attack of rheumatism, more than one fourth of them have had both diseases previously, and in about 1 case in 20 there is a double complication of acute rheumatic fever and chorea in the same pregnancy.

3. The statistics of Allard from the Baudelocque Clinic show that 25 per cent of women giving a history of adolescent chorea have a recurrence of the disease in subsequent pregnancies.

4. The mortality in the group of cases with a previous history of chorea is 7.3 per cent; with a previous history of rheumatism, 7.4 per cent; with a history of both diseases previously, 6.3 per cent. In the groups giving the opposite history, the rates are 18, 13.5 and 19 per cent, respectively. These figures are impossible of explanation except on the hypothesis that a previous attack of chorea or rheumatism or both confers a relative immunity.

5. There is evidence of heart disease in about one third of the cases, and of cardiac pathology in 87 per cent of those coming to autopsy.

6. There is as much histopathologic evidence in the brain favoring the identity of the two conditions as there is opposed to this view, and there can be no question that in both, the brunt of the attack is borne by the corpus striatum.

7. The tendency of the disease to greater severity and a more prolonged course when complicating pregnancy would be expected, *a priori* and is in line with the behavior of other acute or chronic infectious processes under the same circumstances.

8. The symptoms and usual complications are identical.

The prognosis is much less grave than has hitherto been believed and seems to be improving as the mortality rate of 12.7 per cent since 1900 is one half of that obtaining prior to 1880.

The best treatment for the chorea theoretically and from the standpoint of results obtained consists of "rest, seclusion, careful feeding and gentle discipline" (Wall and Andrews). Nerve sedatives and morphine may be used, but sparingly and with great discretion.

In mild cases there is undoubtedly no reason for therapeutic abortion. In severe cases the statistical evidence fails to show better results with intervention than without; in fact, the reverse is true. If resorted to at all, intervention should be by the induction of premature labor or abortion and, except in rare instances, not by immediate operative delivery, as the mortality in these procedures is about 50 per cent. Its most likely indication would seem to be in the case in which the patient is getting progressively worse, despite treatment, but before fever, leukocytosis, etc., give evidence of active and generalized infection; under the latter circumstances, it apparently does nothing but hasten the fatal outcome.

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ASSOCIATION OF INFECTIOUS ASTHMA AND ARTHRITIS

FROM THE POINT OF VIEW OF BACTERIAL ALLERGY *

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In a recently reported study of four hundred adults with asthma, 47 per cent were found to be insensitive to the usual soluble proteins. There was reason to believe that in this group the asthma was an expression of allergy accompanying infection resident in foci of the respiratory tract, in contradistinction to [illegible] groups in which atopic hypersensitiveness, as well as infe[illegible]ycu a rôle. In the entire series of four hundred patients, t[illegible]e were nine in whom, in addition to asthma attacks of arthritis developed.

The ages of these patients varied from 36 to 59. Six were females and three, males. The character of the arth[illegible]itis was migratory, affecting the wrists, fingers, shoulders, ankles, etc. It was accompanied by moderate redness and swelling and pain on motion, and sometimes persisted for several weeks. The body temperature was not elevated. With the exception of three of our cases in which roentgen examination revealed mild proliferative changes in one joint as a rule (the spine or knee), probably due to secondary static influences, no sequelae were noted in any other affected joints.

In five of these patients, foci of infection constituted the sole etiologic factors for the asthma as well as the joint manifestations. In the remaining four there was a coexistent atopic hypersensitiveness to substances such as ragweed, goose feathers, dog hair and rabbit hair, to foods and also to dust. Elimination of these atopens alone influenced neither the asthmatic nor the arthritic attacks. Therefore it seemed that infection in the sinuses and lungs was the exciting cause of both the asthma and arthritis. This theory was proved by the fact that following the evacuation of pus from the infected antrums and the successful treatment of the diseased ethmoids, by means of tampons, mild silver protein, U. S. P., irrigation, etc., and after the recession of the more

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TABLE 1.—*Association of Asthma and Arthritis*

Case	Age	Past History	Roentgenogram of Sinuses	Roentgenogram of Chest	Skin Tests	Arthritis	Treatment	Course and Results
1	47	Admitted 4/28/25; asthma 14 years throughout year	6/18/30, cloudiness of ethmoids and left antrum	Partial consolidation of lower lobe of right lung with considerable fibrosis due to an unresolved pneumonia	Ragweed, short	6/8/27, migrating polyarthritis for 8 weeks; "episcleritis" 6/18/30; arthritis recurred	Evacuation of pus in left antrum 6/18/30	Arthritis receded; asthma improved
2	51	Admitted 1924; asthma 20 years	Pansinusitis; 3/31/31, pansinusitis	Negative; clinical bronchitis	Negative	1/5/26, right shoulder, wrists, sacrum and spine; 3/3/31, recurrent polyarthritis	11/28/27, partial ethmoidectomy; sinuses infected	Arthritis subsided; well till 1930; under treatment for sinuses; 6/6/31, arthritis improved
3	49	Admitted 1922; asthma 13 years; worse in winter	Negative; purulent ethmoiditis clinically	Negative; clinical bronchitis	Goose feathers	Both knees and left wrist, 11/11/25	Irrigation and tampons	12/16/25, arthritis subsided
4	54	Admitted 9/2/27; asthma 18 years	Negative	Unresolved pneumonia	Feathers and dust	Right knee	Typhoid vaccine	Improved
5	36	Admitted 5/26/26; asthma 8 years	Ethmolditis	Negative	Negative	3/16/28, polyarthritis	Local nasal treatment	6/6/28, arthritis receded; asthma improved
6	57	Admitted 6/6/28; asthma 6 years	Left antrum cloudy	Unresolved pneumonia in both lower lobes	Negative	Polyarthritis; meralgia paresthetica, 9/12/28	Evacuation of pus from both antrums	Asthma improved, 2/20/29; arthritis receded
7	36	Admitted 5/3/26	Negative	Unresolved pneumonia of bases of both lungs 4/6/28	Negative	7/27/27, shoulder, elbows, wrists and fingers; right sciatica	Typhoid vaccine	3/12/28, remission of asthma; exacerbation of arthritis; 7/20/28, joints better; 8/12/29, no asthma; migrating arthritis; 8/28/30, asthma well; arthritis subsided; roentgenogram of chest negative
8	59	Admitted 6/5/25; asthma 50 years; pleuropneumonia 1919; influenza 1923; influenza 1929	10/19/27; pansinusitis 4/6/28	Unresolved pneumonia of base of left lung	Negative	11/11/27, polyarthritis; 12/7/28, arthritis left knee; spondylitis of thoracic spine	Evacuation of pus from antrum; typhoid vaccine	Arthritis and asthma improved
9	52	Admitted 2/25/31; asthma 4 years; 1918, bronchitis; 1927, asthma began	Cloudiness of right ethmoids at both antrums	Negative	Dog hair, rabbit hair, cat hair, foods	1917, polyarthritis; 1927, polyarthritis	Evacuation of pus from antrums	Improved during summer of 1918; asthma subsided 3/4/31; arthritis recurred

recent pulmonary focus of infection, the arthritis subsided completely in eight of the nine cases. The asthmatic attacks became milder and diminished in frequency, and the harrassing cough ceased almost entirely.

During the warm weather all residual symptoms referable to both conditions disappeared, indicating the general beneficent effect of temperature and climate on chronic respiratory infections and their complications.

Additional unusual features noted were episcleritis in case 1, diagnosed by the ophthalmologist as evidence of a "rheumatic diathesis," meralgia paraesthetica of the right leg in case 6, and sciatica on the right side in addition to the arthritis in case 7. Comparison of the duration of the asthmatic and arthritic manifestation are shown in table 2.

It is evident from table 2 that a number of years had intervened between the onset of the asthma and that of the joint manifestations.

TABLE 2.—*Comparison of Asthmatic and Arthritic Manifestations*

Case	Age	Duration of Asthma	Duration of Arthritis
1	47	14 years	2 years
2	51	20 years	4 years
3	49	13 years	1 year
4	54	18 years	1 year
5	36	8 years	3 months
6	57	6 years	1 year
7	26	18 years	2 years
8	59	50 years	2 years
9	47	13 years	4 years

If one assumes that as in asthma, an allergic mechanism is accountable for arthritis, the explanation for the delay may lie in the prolonged period necessary to set this secondary shock tissue into action in a system in which the lung was the dominant primary shock organ. The occurrence of several shock tissues as the seats of allergic reactions is not uncommon in the human being. The ascendancy of one over another is equally frequent. Thus a patient who continually has asthmatic seizures from eating eggs may only occasionally have urticaria from the same agent. This is in contrast to the findings in the lower animals in which, as a rule, only one type of shock tissue is found. In the guinea-pig, it is always the pulmonary system; in the rabbit, the circulatory system, and in the dog, the liver is the so-called shock organ involved in anaphylactic reactions.

The transient suppression of one shock organ during the supremacy of another is further exemplified in cases 7 and 9, in which the asthmatic seizures alternated with the attacks of arthritis and vice versa. In case 7, in which both were due to residual pneumonic infiltrations, the recession of the pulmonary focus was succeeded by the subsidence of the asthma as well as the arthritis.

In case 9, the asthmatic attacks ceased following the treatment of the purulent antrums, but a fresh attack of arthritis of the great toe of the right foot brought this patient back to the clinic. In reviewing this case we found that, in addition to the sinus disease there was an underlying atopic hypersensitiveness to inhalants as well as to numerous foods, which in all probability was fundamentally responsible for the secondary infection. In 1914, the patient had an intranasal operation, but in spite of it he continued to contract so-called colds. In 1917, he had an attack of polyarthritis which lasted for three months.

With the onset of the warm weather the arthritis receded, but the nasal condition began to bother the patient again. This condition persisted until 1918, when so-called bronchitis developed, which lasted throughout the year until the winter of 1927, when a recurrence of arthritis occurred. Simultaneously the asthmatic attacks appeared for the first time. The arthritis again subsided with the return of summer. On the last admission he complained of asthma which, as already noted, was controlled after irrigation of the sinuses, only to be succeeded by the arthritis. Whether food sensitiveness plays an additional rôle in the arthritis of this patient or whether, as seems more probable, the sinusitis was incompletely eradicated, it is impossible to state at present.

The striking sequence of events in these cases, the identification of a common focus of infection responsible for the asthma and arthritis and the elimination or recession of the infection being followed in most patients by amelioration of the asthma and disappearance of the arthritis leads us to the conclusion that both conditions are mediated by the same agent, and we suggest that a similar mechanism, namely, bacterial allergy, may be operative in both.

In examining this conception it is important to have a clear idea of what we mean by allergy and, especially, bacterial allergy.

On account of its varied connotations, a definition of allergy is a most difficult task. To facilitate the understanding of its current status, a brief review of its evolution may be timely.

Originally employed by Pirquet [1] in 1906 to designate "Reaktionfähigkeit" or the reacting capacity of actively sensitized and artificially prepared animals to the original antigen, it was used later by the same author to describe reactions of man to foreign substances. Cooke and Vander Veer [2] and Spain,[3] however, by careful clinical studies have been able to demonstrate that certain persons in this allergic group are radically different from normal persons, by heredity, and possess the

1. Pirquet, C.: Allergie, München. med. Wchnschr. **53**:1457, 1906; Allergy, Arch. Int. Med. **7**:259 (Feb.) 1911.
2. Cooke, R. A., and Vander Veer: J. Immunol. **8**:163, 1923.
3. Spain, W. C., and Cooke, R. A.: J. Immunol. **9**:521, 1924.

faculty of spontaneously reacting to foreign proteins; in other words, they are naturally hypersensitive. Prausnitz and Kustner [4] and de Besche [5] found that the serum of such patients contains specific bodies (reagins) capable of sensitizing the normal human skin. Reagins of the same character have subsequently also been found in artificially sensitized patients. Nevertheless, Coca [6] felt that in order to differentiate those artificially sensitized from those who are spontaneously sensitive, the latter should be designated as atopic.

As normal persons who do not possess atopic characteristics may on artificial contact with certain foreign substances, such as horse serum or bacterial proteins, acquire and manifest similar reactions, that is, reactions characterized by an anaphylactic-like mechanism seen in atopic patients or in animals, such persons may also be designated as allergic.

The term allergy for the present therefore, in contrast to atopy, may serve as a generic term to indicate sensitiveness of the atopic and acquired type to foreign proteins, chemical substances and bacteria. Whether the ability to acquire sensitiveness is universal or requires a special predisposition is difficult to state with certainty. In view of the fact, however, that the same agent that induces allergic manifestations in one individual does not do so in another seems to imply that peculiar constitutional factors play a rôle.

These factors are evidenced not only in localized cellular tissues, but embrace the humoral as well as the neural structures, particularly the vegetative nervous system and its various ramifications.

In asthmatic persons the autonomic system is particularly vulnerable. The vagus and its reflex paths may so readily be affected by various exciting agents that the lung is readily thrown into shock. The occurrence of a similar phenomenon in the guinea-pig's lungs caused Doerr [7] to call it "the shock organ." Coca,[6] transposing this idea to the human being, designated tissue manifesting altered reactivity as "shock tissue." That in the atopic patient a single substance like shell fish may simultaneously induce reactions of several shock tissues, such as the lung, skin and joints, inducing asthma, urticaria and arthritis, is well known. Similar effects may follow in persons whose sensitiveness is acquired. To demonstrate such sensitiveness to soluble proteins by means of skin tests, etc., is comparatively easy. However, in dealing with chemical agents or bacteria, numerous difficulties present themselves.

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4. Prausnitz and Kustner, H.: Centralbl. f. Bakt. **86**:160, 1921.

5. de Besche, A.: Am. J. M. Sc. **166**:265, 1923.

6. Coca, A. F.: Atopy: The Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928.

7. Doerr, R.: Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap. **5**:71, 1922.

In the study of allergy to bacteria the question naturally arises: What is it that sensitizes the individual, the whole organism, the so-called soluble specific substance, the somatic proteins or the toxins? It is obvious that the primary effects of toxins must be taken into account in interpreting results in disease in human beings. Toxins have thus far not been proved to be responsible for allergic manifestations. On the other hand, Wells [8] made the suggestion that toxins may represent a combination of a pure toxic radical which does not give a positive reaction to chemical tests for proteins and attached proteins, and that such radicals may split off more or less completely from their particular protein vehicle and reunite with the proteins of the animals into which they are injected, thereby serving as a sensitizing antigen. Analogies for this process may be found in the reactions taking place between nonprotein substances, such as iodine, salicylates, arsenic, etc., which are supposed to unite with the individual's own protein, thereby converting them into foreign proteins which serve as antigens. Landsteiner's [9] well known work with the azoproteins may serve as an example of such synthesis in vitro.

Convincing proof, however, of the actual occurrence of such combinations with toxin is lacking. As a matter of fact, the work of Zinsser and Grinnell [10] and of Dochez and Stevens [11] tends to disprove such an antigenic rôle. Dealing with streptococci, these authors were able to segregate a neutralizable toxin, and thus demonstrate that the hypersensitiveness obtained was due to a nonneutralizable bacterial product. This naturally leads one to other bacterial products as sources of allergic reactions.

In 1925, employing streptococci, Zinsser and Grinnell [10] were able to sensitize guinea-pigs and subsequently elicit skin sensitiveness with streptococcus material, especially Dick filtrate, corresponding, in manner of production and in important attribute of heat stability, to tuberculin. They suggested at this time that such streptococcus allergy might have some relationship to certain forms of arthritis in which the association of sterile joint conditions with streptococcus infection had been recognized clinically. Sensitizing guinea-pigs with hemolytic streptococci as well as pneumococcus autolysates in 1927, these workers again were able to obtain skin sensitivity more severe than that seen in the most extreme reaction to tuberculin. In a number of their guinea-pigs, when satisfactory skin sensitization had been obtained with the pneumo-

8. Wells, H. G.: The Chemical Aspects of Immunity, New York, The Chemical Catalog Company, 1925.

9. Landsteiner, K.: Biochem. Ztschr. **104**:280, 1920; J. Exper. Med. **39**:631, 1924.

10. Zinsser, H., and Grinnell, F. B.: J. Immunol. **10**:725, 1925.

11. Dochez, A. R., and Stevens, F. A.: J. Exper. Med. **46**:487, 1927.

coccus autolysate, this material injected into the joints caused the development of swollen joints, whereas in normal controls as well as in animals in which skin tests were negative, showing an absence of allergy, the joints were uninvolved. Zinsser and Grinnell felt that many substances analogous to their pneumococcus autolysates may be liberated from the bacteria within the infected body in the case of organisms not subject to test tube autolysis, and suggested that this process in the course of pneumonia might occur in the lungs and furnish sensitizing antigens in considerable quantities. If this is so, it may serve to explain the infectious asthma that we have described in association with unresolved pneumonia.

The more recent work of Francis and Tillet [12] has substantiated to a great extent the early observations of Zinsser and Grinnell. By injecting type-specific polysaccharides of the pneumococcus capsule intradermally into patients with pneumonia following the crisis, they were able to demonstrate definite cutaneous reactions in certain instances with carbohydrates homologous to the type of pneumococcus causing infection in the patient. The character of the cutaneous reaction is urticaria-like in appearance, and runs its course in one or two hours. The reaction caused by the pneumococcus protein, on the other hand, is similar in appearance and evolution to that evoked by tuberculin. Such positive reactions reach their maximum intensity within about twenty-four hours after injection, and sometimes require from three to four days to subside completely. The capacity of the patient to react to the protein bears no relation to the type of pneumococcus causing the infection.

Fatal anaphylactic shock with nitrogen-free bacterial carbohydrates of pneumococcus types II and III in guinea-pigs passively sensitized with the precipitating serum of rabbits immunized with pneumococci of the homologous type has been obtained by Avery and Tillet.[13] Tomcsik [14] and Tomcsik and Kurotchkin,[15] isolating specific carbohydrate material from B. lactis-aerogenes, found that the pneumobacillus and a yeast were likewise able to induce fatal anaphylactic shock as well as positive uterine contractions, according to the Schultz-Dale technic, in passively sensitized guinea-pigs. Similar results have been reported by Lancefield,[16] working with streptococcal carbohydrate substance in guinea-pigs passively sensitized with antistreptococcal serum.

12. Francis, T., and Tillet, W. J.: J. Exper. Med. **52**:561, 1930.
13. Avery, O. T., and Tillet, W. J.: J. Exper. Med. **49**:251, 1929.
14. Tomcsik, K.: Proc. Soc. Exper. Biol. & Med. **24**:379, 1927.
15. Tomcsik, K., and Kurotchkin, T. K.: J. Exper. Med. **47**:379, 1928.
16. Lancefield, R. C.: J. Exper. Med. **47**:379, 1928.

In the field of infection with hemolytic streptococci, bacterial allergy is found in certain phases of scarlet fever and erysipelas. This has been shown by the work of Dochez and Stevens,[11] Birkhaug,[17] Zinsser and Grinnell,[10] Mackie and McLachlin[18] and Kirchner.[19] In these studies, although the primary inoculation was frequently made with cultures of the respective streptococci, the test substance was a broth filtrate or some bacterial fraction.

Experiments with various nonhemolytic streptococci have been carried out by Derick, Hitchcock and Swift[20] in connection with their studies in rheumatic fever which led them to the conclusion that focal infection resulting from inoculations with nonhemolytic streptococci may be followed by a state of hypersensitiveness. This is evidenced by "increased skin reactivity to reinoculation with small doses of streptococci, by marked reactivity of the scarified cornea to installation of streptococci into the conjunctival sac, and by the death of many of the animals following intravenous inoculations with cultures in amounts well tolerated by normal animals."

Finally, the stimulating investigations of Zinsser[21] on tuberculin hypersensitiveness, which may give a clue to the elucidation of the Poncet type of tuberculous arthritis, have recently been further elaborated by Lewis and Seibert.[22] These workers have been able to show that proteins isolated from filtrates of acid-fast bacterial cultures on synthetic mediums are actively anaphylactogenic. By the use of the anaphylactic reaction they were also able to establish a definite antigenic relationship between the three types of tubercle bacilli proteins, and to sensitize passively normal guinea-pigs with precipitating serums from guinea-pigs immunized with tuberculin protein.

From this brief summary of recent work on bacterial allergy, it is obvious that evidence is rapidly accumulating to the effect that the allergic state is part of the immunologic mechanism accompanying infection. Before antibodies have been accumulated to any extent in the circulation, the phenomenon is mainly cellular; the first stage expresses itself in an extraordinary irritability of the cell in contact with the antigen. We may say with Zinsser, that "in bacterial allergy we are dealing with sensitization of the body by autolytically liberated

17. Brikhaug, K. E.: J. Infect. Dis. **40**:549, 1927.
18. Mackie, T. J., and McLachlin, D. G. J.: Brit. J. Exper. Path. **8**:129, 1927.
19. Kirchner, O. T.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **55**:157, 1928.
20. Derick, C. L.; Hitchcock, C. H., and Swift, H. F.: Canad. M. A. J. **20**: 349 (April) 1929.
21. Zinsser, H.: J. Exper. Med. **34**:495, 1921.
22. Lewis, J. H., and Seibert, F. B.: J. Immunol. **20**:201, 1931.

antigenic substances, which are absorbed from any focus in which bacteria reacted to inflammatory tissues, and as a result of which the body is rendered subsequently sensitive to contact with the same autolytic products, whether they are liberated and absorbed from a chronically existent focus, or from an identical infection subsequently acquired."

In the clinic, interpretation of bacterial allergy in much more difficult. The complex reactions accompanying immunologic processes in the human being are as yet not sufficiently elucidated. Positive skin tests with bacteria or their products do not always establish an etiologic relationship between the organism and the disease under investigation. The reason may perhaps be found in the following facts: 1. Proper antigenic fractions of the incriminating bacteria are not yet available. 2. There may be a relationship between protein fractions of certain bacteria and heterologous organisms that may give rise to confusing reactions. 3. Invasion with living bacteria may so alter the tissues that secondary antigens may develop and be responsible for allergic manifestations. 4. The occurrence of minor secondary bacterial infections in the respiratory passages or the continuous focal presence of certain ubiquitous organisms in the hosts may be responsible for positive reactions on intradermal injection, so that reactions with so-called specific antigens may be obtained in normal persons and be of no special significance.

In view of such difficulties, conclusions as to the nature of this syndrome must be based on a clinical interpretation of symptoms in the light of established experimental and empiric data. The evidence at hand that leads us to suspect that the arthritis may be of the same nature as the asthma rather than coincidental is therefore partly circumstantial and partly factual. It is founded (1) on analogies of essentially atopic syndromes following the injection of soluble foreign proteins, such as horse serum, etc., in which asthma, arthritis and urticaria may occur; (2) on the fact that infectious asthma due to allergy to bacteria, which is admittedly an accepted clinical entity, may be associated with similar symptoms of arthritis; the allergic nature of this condition is further supported by the observations of Zinsser[23] to the effect that "experimentally, in bacterial allergy, it appears that sensitiveness of joints can be demonstrated as to some extent parallel to general sensitiveness"; (3) on the findings that the same foci remote from the joints were responsible for the asthma as well as for the arthritic symptoms; this is in line with the work of Swift, Hitchcock and Derick which indicated

23. Zinsser, H.: The Bacteriology of Rheumatic Fever and the Allergic Hypothesis, Arch. Int. Med. **42**:301 (Aug.) 1928; Bull. New York Acad. Med. **4**:351, 1928.

that focal infection gives rise to a state of hypersensitiveness; (4) on the observations that none of the patients showed toxic manifestations due to the chronic foci; they were ambulatory, and their temperatures rarely exceeded 99 F., and (5) on the marked relief from the asthmatic attacks and the complete disappearance of arthritis following the elimination of the responsible foci of infection in eight of the nine cases.

As a consequence of these findings it can be stated that certain persons may develop sensitiveness to bacterial infection, the effects of which may be manifested in one or more particular distant sites, the respiratory tract or the joints. The clinical manifestations may be asthma or recurrent nasopharyngeal symptoms, such as vasomotor rhinitis or arthritis. The presence of two "shock organs" in the sense of Coca in the same person may induce involvement in both. Atopic sensitiveness may coexist, and when latent, may be brought to the fore by an acute bacterial infection; thus, it may be primary or secondary. In our experience we have frequently noted that an infection in the upper part of the respiratory tract may evoke latent atopic hypersensitiveness.

SUMMARY

In a study of bronchial asthma due to hypersensitiveness to infection, nine cases were observed in which attacks of arthritis developed. The arthritis was migratory, affecting various small and large joints, and was accompanied by redness, swelling and pain on motion, but practically no fever. The duration of arthritis varied from two to four years, whereas that of asthma was from six to fifty years.

In five of the patients, foci of infection in sinuses and lungs constituted the only etiologic factors of the asthma and joint manifestations. In four, besides infection there was a coexistent atopic hypersensitiveness to substances such as ragweed, goose feathers, etc. Simple elimination of these atopens had no influence on either the asthma or the arthritis. Evacuation of pus from antrums, treatment of ethmoids and the consequent recession of the pulmonary focus caused complete subsidence of the arthritis in eight of the nine cases, while the asthmatic seizures diminished in frequency and severity in each instance.

A consideration of recent accumulating evidence of bacterial allergy accompanying infectious conditions such as scarlet fever, rheumatic fever and its arthritis, tuberculosis, etc., leads us to the conclusion that the allergic state is part of the immunologic mechanism accompanying infection.

In asthma induced by a chronic focus of infection, bacterial allergy is an admittedly accepted mechanism. Coexistent arthritis due to the same focus is in all probability an expression of a similar reaction in

allergic persons in whom the lungs are the primary and the joints the secondary shock tissues.

In the present state of knowledge direct proof of bacterial allergy by means of skin tests is difficult to obtain. Interpretation of the nature of the asthma-arthritis syndrome in our patients on the grounds of allergy to bacteria is based, therefore, on known accepted experimental and clinical facts as well as on analogies to similar clinical pictures in the domain of protein hypersensitiveness, such as serum sickness, etc.

Correspondence

"EXPERIMENTAL AGRANULOCYTOSIS"

To the Editor:—In the January, 1932, issue of the ARCHIVES OF INTERNAL MEDICINE is an article entitled "Experimental Agranulocytosis," by B. M. Fried and William Dameshek.

This article implies by title and indicates to the casual reader that the disease, agranulocytosis, has been produced by the intravenous injection of Bacillus pyocyaneus into rabbits.

It is the purpose of this communication to correct any such impression and to call attention to the fact that the results obtained by the authors may be duplicated by a wide variety of substances, including milk, nonspecific proteins, dead and living bacteria and various types of inert, finely divided material.

In the interpretation of their results, the authors evidently overlooked the fact that a pronounced temporary granulocytopenia results from the intravenous injection of any of the foregoing substances. This has long been recognized by research workers and those familiar with hematologic reactions in rabbits. Wells (Leucopenia and Leukocytosis in Rabbits, *J. Infect. Dis.* **20**:219, 1917) injected dead typhoid bacilli, streptococci and staphylococci into rabbits, and concluded: "There occurs regularly in the blood, following intravenous injections of foreign proteins a marked reduction of leukocytes, and after several hours, a marked increase of leukocytes." In connection with this quotation, it is significant that Fried and Dameshek killed most of their animals at the end of twenty, thirty, forty and seventy minutes, respectively, at times when the leukopenia was marked. Had they been allowed to live, a leukocytosis probably would have developed.

Doan and his associates (Doan, C. A.; Zerfas, L. G.; Warren, S., and Ames, O.: A Study of the Mechanism of Nucleinate-Induced Leucopenic and Leucocytic States, with Special Reference to the Relative Rôles of Liver, Spleen and Bone Marrow, *J. Exper. Med.* **47**:403, 1928) showed clearly that in normal rabbits sodium nucleinate induces an immediate, temporary leukopenia due to accumulation of the granulocytes in the spleen, and that this then is followed by leukocytosis, whereas in splenectomized rabbits, the leukocytosis is immediate.

Since the publication of the work by Fried and Dameshek, I have duplicated all of their reported experiments, using dead typhoid bacilli, and in the larger doses have produced a degree of granulocytopenia, amounting in some instances to complete absence of granular cells. That is, if the term agranulocytosis is justified by these authors, it can be produced as well with dead typhoid bacilli or any other dead bacilli as with living B. pyocyaneus.

I wish to differ therefore from the implication by title and text that agranulocytosis was produced by these workers, and to call attention to the fact that they evidently overlooked the well accepted leukopenia that temporarily follows the injection of such substances. If desired, I will be glad to submit records of animal experiments duplicating their findings with dead typhoid bacilli.

Also, in connection with the subject of agranulocytosis, I should like to offer a criticism of the proposed term "hypogranulocytosis" used by Conner and his associates in the same issue of the ARCHIVES OF INTERNAL MEDICINE (Conner, H. M.; Margolis, H. M.; Birkeland, I. W., and Sharp, J. E.: Agranulocytosis and Hypogranulocytosis, ARCH. INT. MED. **49**:123 [Jan.] 1932).

This term, first used by Weiss, should be abandoned because of its obvious incorrectness, meaning "a decreased number of increased granulocytes." A better one, as proposed by Roberts and myself (Roberts, S. R., and Kracke, R. R.: Agranulocytosis: Its Classification, *Ann. Int. Med.* **5**:40, 1931), and consistent with accepted terminology, would be "granulopenia."

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To the Editor:—In our studies on experimental agranulocytosis we used Salmonella suipestifer and not Bacillus pyocyaneus, as mentioned by Roy R. Kracke. The purpose of our studies was to determine the possible similarity between the *blood picture* as seen in agranulocytosis in man and that found in *one form* of experimental sepsis in rabbits. Our experiments were undertaken in connection with statements to the effect that human agranulocytosis is a disease *sui generis*. The experiments have shown that granulocytopenia may be observed in this form of experimental sepsis. However, no claims were made that the micro-organism used in our experiments was the essential cause of the disease in man or that other bacteria might not produce the same disease in the rabbit.

Simultaneously with our paper in the ARCHIVES, there appeared an article by Roy R. Kracke, bearing the identical title that ours did: "The Experimental Production of Agranulocytosis" (*Am. J. Clin. Path.* **2**:11 [Jan.] 1932). It is interesting that in this article, to which there is no reference in his letter, Kracke is emphatic in stating that "subcutaneous injections of benzene and olive oil . . . resulted in the development of clinical agranulocytosis in rabbits."

We are aware, as is Kracke, that a pronounced temporary granulocytopenia may be induced in the rabbit by hematogenous injection of a number of substances and of various bacilli. Thus, in quoting unpublished data obtained by us on the peripheral blood picture of rabbits infected with tubercle bacilli, one of us (Dr. Fried) stated (*Arch. Path.* **12**:689 [Nov.] 1931) that "studies on the peripheral blood of rabbits infected with tubercle bacilli reveal that the infection is followed by an almost instantaneous leukopenia."

Those who have read our paper in the ARCHIVES have noticed that only a small group of our animals were killed shortly after injection of bacteria in order to study the response of their bone marrow. The majority of rabbits, of which only a few illustrative protocols were given, lived for several days.

Kracke states that he was able to induce agranulocytosis in rabbits with dead typhoid bacilli, also quoting Wells and Doan who produced temporary pronounced granulocytopenia with staphylococci, streptococci and other organisms and substances. It is thus of interest that on page 13 of his article, to which we have referred, the following statement is made: "I have injected various organisms isolated from the blood-stream of patients with the disease (agranulocytosis) and in each instance have failed to depress the leukocyte count."

We, too, would not object to replacement of the term agranulocytosis by that of "granulocytopenia" (and not granulopenia, as suggested by Kracke) or of "malignant neutropenia," as suggested by V. Schilling and used recently by Dameshek and Ingall (*Am. J. M. Sc.* **181**:502 [April] 1931) in a clinical report of this condition.

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Book Reviews

Cancer and Race: A Study of the Incidence of Cancer Among Jews. By Maurice Sorsby. With a preface by Lt. Col. F. E. Fremantle. Price, $3. Pp. 120. New York: William Wood and Company, 1931.

This is a distinct contribution to the literature on cancer; it is of far greater value than many statistical studies published in the past, because the author recognizes the limitations of the validity of his statistical material and refrains from making unjustifiable deductions therefrom. The theme is set forth in a quotation from Roger Williams' book on the "Natural History of Cancer": "The Jewish race being widely scattered throughout the world and the conditions of existence of its various communities being accordingly diverse, is admirably circumstanced for illustrating the comparative importance of race factors *versus* conditions of existence, in determining the incidence of cancer." Furthermore, the Jewish people have in certain cities to a large extent maintained the pure strain of their race. They have kept, to a considerable point of detail, accurate returns over a long range of years. Their ritual laws and habits, moreover, have established definite conditions that differentiate them from the other communities in which they live, and these conditions might be expected to have an influence on the incidence of cancer. This difference and its bearing on the causation of cancer have long been recognized and widely discussed. Under the Jewish Health Organization of Great Britain, Dr. Sorsby has carried out a careful and comprehensive investigation of the subject. The results are presented in this book and will be found both interesting and instructive.

A consideration of the mortality from cancer among Jews reveals that the total mortality varies in different Jewish communities, tending to approach that of the non-Jews of that particular city; i. e., it follows a geographic rather than a racial distribution. Also, the incidence of cancer per organ in some respects shows striking differences among Jews compared to non-Jews.

The frequently reported observation that cancer of the uterus is relatively infrequent in Jewish women as compared with the Gentile women of the same communities is fully corroborated, and is checked by the demonstration that cancer of the breast does not show any appreciable difference, while cancer of the gastro-intestinal tract seems to be more frequent among the Jews. Cancer of the penis is almost never recorded in Jewish patients, and as the same infrequency is observed in the circumcised Mohammedans, this rite is given credit for the immunity rather than any racial difference. Therefore, the low incidence of cancer of the cervix is also thought to depend not on any racial property, but solely on local conditions, probably the sexual hygiene of the Mosaic code, of which Sorsby says, "It is the lasting achievement of the Mosaic code that it has taught Jewish women that vaginal discharges are essentially pathological and avoidable."

While this conclusion may be correct, and racial characters are not responsible for this peculiarity, we have before us the apparently equally marked exemption of Japanese women in respect to cancer of the breast, without the benefit of Mosaic law.

Asthma and Hay-Fever in Theory and Practice. By Arthur F. Coca, Mathew Walzer and August A. Thommen. Price, $8.50. Pp. 850. Springfield, Ill.: Charles C. Thomas, 1931.

This book is written in three parts. Part one consists of 117 pages and was written by Dr. Coca. In this section, hypersensitiveness, anaphylaxis and allergy are discussed from a theoretical standpoint. The literature is covered thoroughly,

and an attempt is made to clarify many of the terms that have arisen in these fields. A table is presented giving the essential differences between anaphylaxis, atopy, hypersensitiveness of infections, contact dermatitis and serum sickness. These subjects are discussed in great detail from the standpoint of occurrence, age of onset, how established, heredity, mechanism, reaction of the guinea-pig, reaction of the human skin and possibility of desensitization. The last chapter of this section is devoted to the preparation of extracts and solutions for use in testing and treatment in human hypersensitiveness.

Part two is devoted to the consideration of asthma and covers the next 370 pages. Dr. Walzer discusses the early history of the disease, and then at great length writes about the theories of asthma, the pathology, etiology, clinical course and symptomatology, complications and treatment. These subjects are covered admirably and in an interesting manner. The literature has been covered exceptionally well, and, in addition, the author expresses his own views thoroughly. Dr. Thommen assisted Dr. Walzer in writing the chapter on "The Methods of Testing for Hypersensitiveness," and Miss Katherine Bowman assisted in the chapter on "Atopens and Other Excitants." This last chapter is of a great deal of interest because of the detailed discussion of every excitant. References are given for more complete study of each substance.

The third part, devoted to the discussion of hay fever, consists of 300 pages and is written by Dr. Thommen. The history of hay fever is taken up first, and then the essentials of flower structure and the process of pollination are discussed. Before the etiology and mechanism of hay fever are considered, the author describes in the greatest detail all the plants, grasses, trees and weeds that have any bearing on the disease. The practical side of the diagnosis and treatment of hay fever is as well discussed as the theoretical consideration in the earlier chapter. The whole subject is handled in an admirable manner.

The book contains a wealth of information and a bibliography that is hard to surpass. It should be of the utmost value to any student of hay fever and asthma.

Röntgenuntersuchungen am Innenrelief des Verdauungskanals, ein Beitrag zur klinischen Röntgendiagnostik insebesondere von Entzündung, Geschwür und Krebs. By Prof. Hans Heinrich Berg, Chefarzt der medizinischen Klinik der stadtischen Krankenanstalten in Dortmund. Second edition. Price, 50 marks. Pp. 248, with 247 illustrations. Leipzig: Georg Thieme, 1931.

The first edition of this work, published in 1930, is now offered in forty-six more pages and with fifty-four more illustrations. The text is amplified, and more attention is paid to technic and sources of error. The most noteworthy additions pertain to the esophagus, diaphragmatic herniations, the stomach on which an operation has been performed and the colon.

For those who are unfamiliar with the first edition, it may be said that the work is one of the choicest contributions to the literature of gastro-enterology. Berg, an old pupil of Forssell's, pioneered in the systematic roentgenologic examnation of the digestive tube by the use of sufficiently small amounts of barium to bring out the relief picture of the mucosa. His disciples, notably Gutzeit, Albrecht and Knothe, have done much to further its development.

The book begins with a historical review, which is followed by a detailed discussion of technic and of possible errors. The underlying anatomic and physiologic considerations are well presented. Normal conditions are described and pictured. The pathologic changes are critically discussed and beautifully illustrated with excellent reproductions of films and frequently with photographs of the anatomic specimens. It is a pleasure to recommend this classic most highly to all students of roentgenology and gastro-enterology.